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COMBINED MEDICAL AND SURGICAL MANAGEMENT OF CORONARY HEART DISEASE*

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Cornary heart disease is a constant problem to the medical profession. This report concerns a surgical method of therapy which is an effective adjunct to current medical management.

To stem the continuous spread and invasion of this disabling disease, the cardiologist, internist and surgeon should unite their skills to reduce mortality, rehabilitate the cardiac cripple, and return him to social usefulness. A few years ago, statistics recorded more than 325,000 deaths annually from coronary disease in the United States (1). When the deaths from diseases associated with hypertension and congestive failure are added, this appalling number is considerably increased. It will continue to rise with the ever-increasing life span of man.

It is true that diet, heredity, metabolic disorders and estrogenic activity play their respective roles, as coronary heart disease occurs in the young as well as the old; but the exact cause remains a mystery. A diet in which over 40 per cent of the calories is obtained from fats (since infancy), and lack of exercise in later years, are the important etiologic factors. In China, Japan and certain other countries, coronary heart disease is rare. In these countries, over-population results in poverty of the masses and exhaustion of the soil. The majority of the people subsist on sea-foods, lean meats, fresh fruits, vegetables and rice.

Injection studies have shown that in 90 per cent of normal dog hearts, intercoronary anastomoses are inadequate (Fig. 1).

According to Beck and Leighninger (2), a supply of only 4.7 cc. of additional blood per minute is necessary to prevent myocardial destruction beyond an occlusion. Therefore, we and many other investigators endeavored to increase intercoronary and extracoronary anastomoses of the coronary arteries by means of surgical adhesive pericarditis induced by inflammatory agents and abrasives (3–10). The results demonstrated that it was possible to prevent further damage to the myocardium by providing the heart with an additional intercoronary and extracoronary blood supply through vascularized adhesions. In these pericardial adhesions and intercoronary communications, the vessels are extremely narrow,

* Part of the illustrative material in this article was shown at the Scientific Exhibit of the American Medical Association, New York, N. Y., June 1957.

FIG. 2

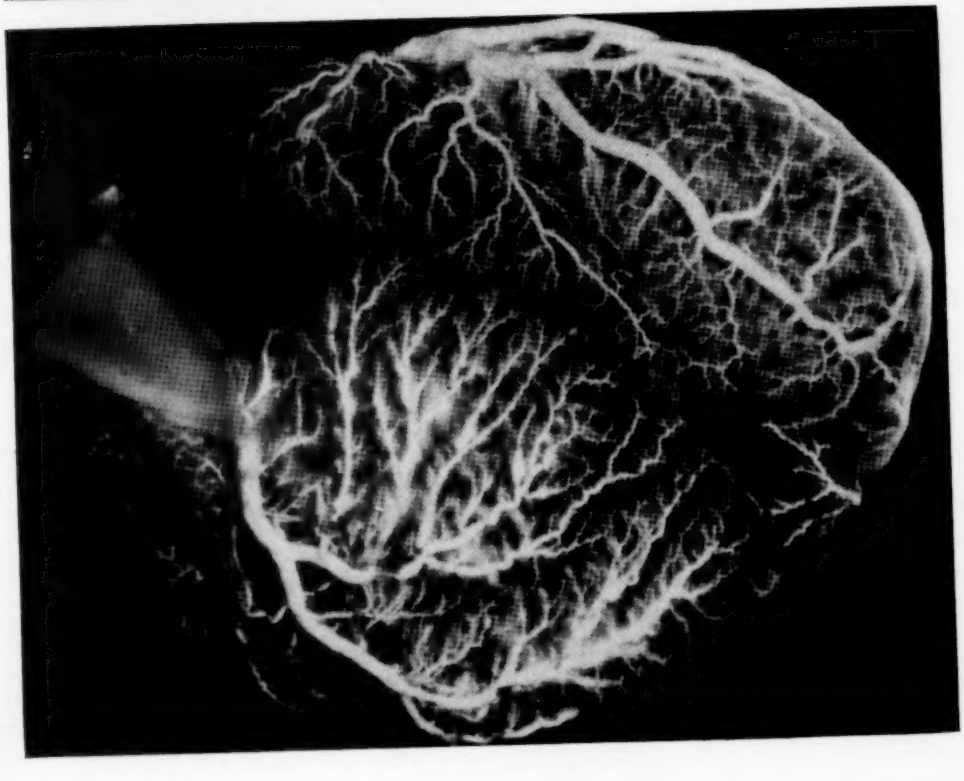

FIG. 1

FIG. 1. Normal dog heart—Showing lack of intercoronary connections between right and left descending coronary arteries. The same is true in 90 per cent of human hearts. (Beck, C.: Unpublished data, reproduced with the permission of the author.)

FIG. 2. Protected dog heart—Showing intercoronary connections between right and left descending coronary arteries one year fol-

resembling capillaries or small arterioles. The sum of their cross-sectional area may be as great or even greater than the cross-sectional area of the coronary arteries themselves. This explains why patients suffer when they have an inadequate blood supply and experience relief when there is an adequate and balanced supply of blood and oxygen (Fig. 2).

When blood and oxygen supplies are adequate and uniformly distributed, the heart is stabilized and protected. Otherwise, death may result—not from massive occlusion of a major vessel or from severe infarction, as most of us have been led to believe, but largely from *ventricular fibrillation*, which is mechanical. Ventricular fibrillation causes 80 to 90 per cent of all coronary deaths, whether or not they be associated with infarction. Only 10 to 20 per cent of such deaths are the result of damage to the cardiac muscle caused by repeated infarcts with resultant congestive failure.

This observation has been confirmed by Yater and co-workers (11) in an analysis of the autopsy findings in 950 cases of sudden death among Army personnel. Only narrowed and sclerotic vessels with no occlusions or infarctions were revealed in 34 per cent of these hearts. Infarction was present in 56 per cent. We agree with Beck (4) that the danger is an unbalanced distribution of blood and oxygen within the myocardium which, in a trigger-like action, produces a disturbance or break in the co-ordinated heart mechanism due to the differences in electrical potentials. The precipitating factor may be only a small ischemic area from an occlusion, an infarct, or a sudden emotional stress causing an overload. This has been verified in our experimental laboratory.

OPERATION AND INDICATIONS

In this report, we present a clinical study of 78 patients treated surgically during the past six years. On our first 40 patients we employed the Thompson procedure (6) exclusively. The last 38 patients were operated upon by our modification of the Thompson (6) and Beck (4) procedures. We use an extrapleural approach to the heart (3). It is safe in properly screened patients. Our present cardiopexy technique yields the best results with a minimal risk. The operative time is approximately one hour.

The operation

A 4-inch incision is made over the left fifth rib, and a 2½-inch section of the costal cartilage is removed. The mediastinal space is exposed by pushing away the pleura beneath the costal cartilage (Fig. 3). The left internal mammary artery and vein are ligated at this time. The pericardium is opened, and a 1 per cent solution of xylocaine (about 5–10 cc.) is sprayed into the pericardial sac (Fig. 4). After a few minutes, the pericardium is held apart by retractors. Using Beck burrs, the pericardium is then scarified thoroughly, with the exception of the extreme posterior portions (Fig. 5).

The same procedure is repeated with the epicardium—being more gentle and careful in order to avoid injury to the coronary vessels. The pericardium is thoroughly dried by suction (Fig. 6). Then, by means of a series of atomizers, magnesium silicate (several drams) is sprayed into every nook and corner of the pericardium (Fig. 7).

The pericardium is closed loosely and the skin may be closed without drainage. On the other hand, if the pleura has been injured during the procedure, a closed water-bottle drainage may be used for forty-eight hours after inserting a catheter at about the sixth or seventh interspace.

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FIG. 2. Protected dog heart—Showing intercoronary connections between right and left descending coronary arteries one year fol-

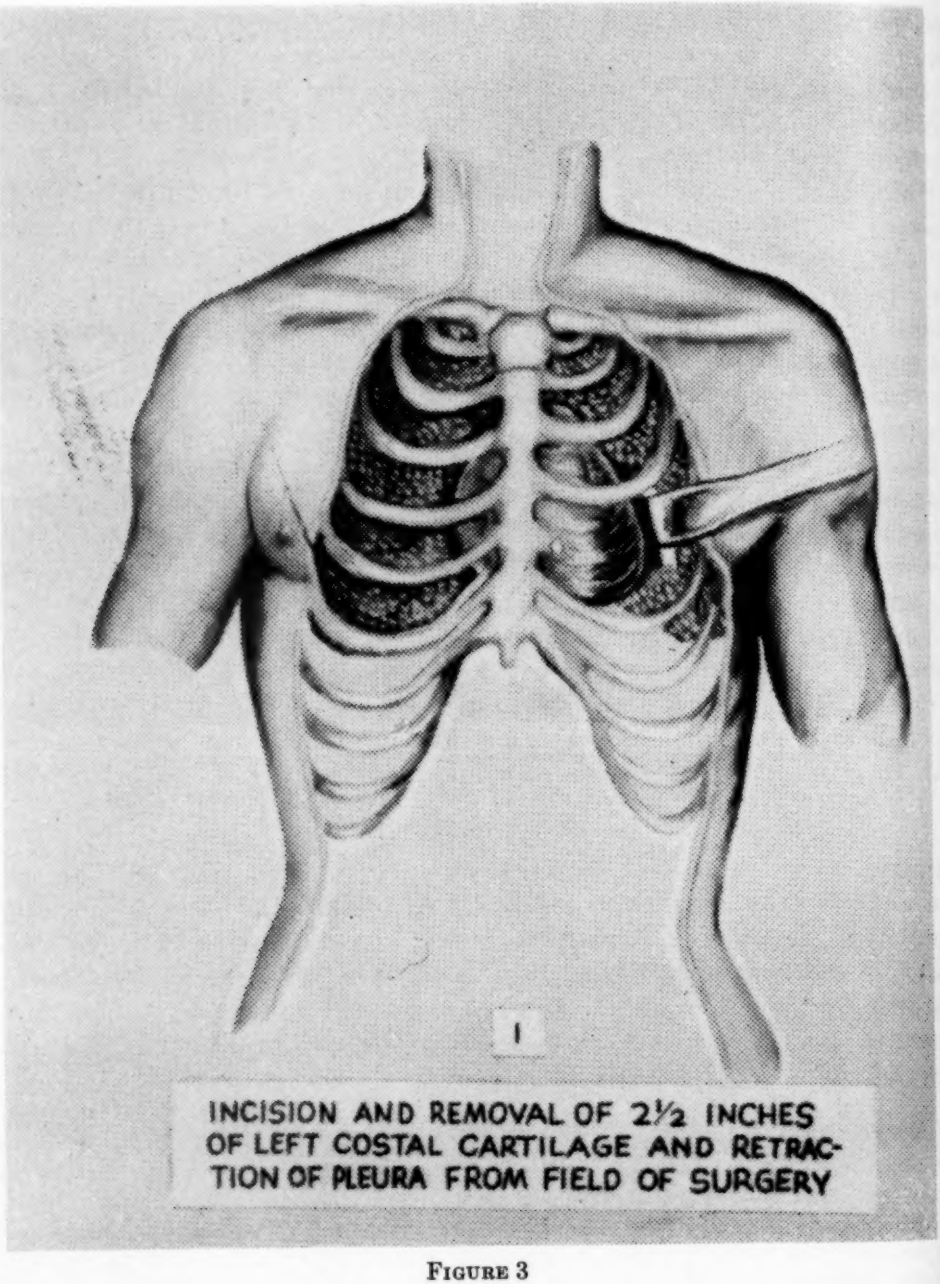

FIGURE 3

The entire procedure is guided by our own observations, the report of the anesthesiologist, and the report of the cardiologist as he monitors the electrocardiograph and electrocardioscope.

Immediately following the operation, an x-ray film is taken of the chest (in the operating room) to ascertain the degree of lung expansion, and whether there are any collapsed areas, or any air in the pleural cavity.

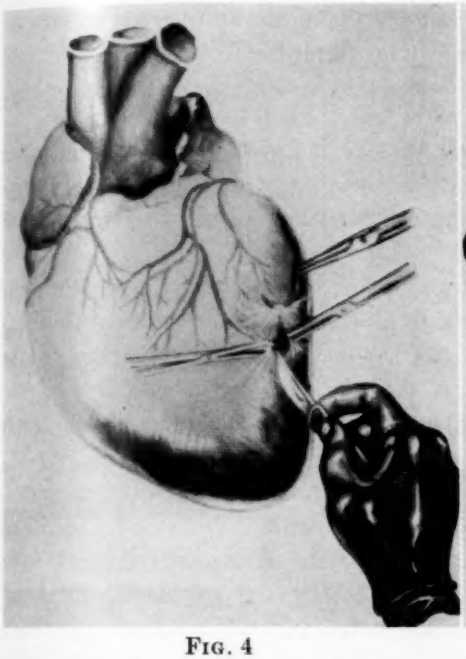

FIG. 4

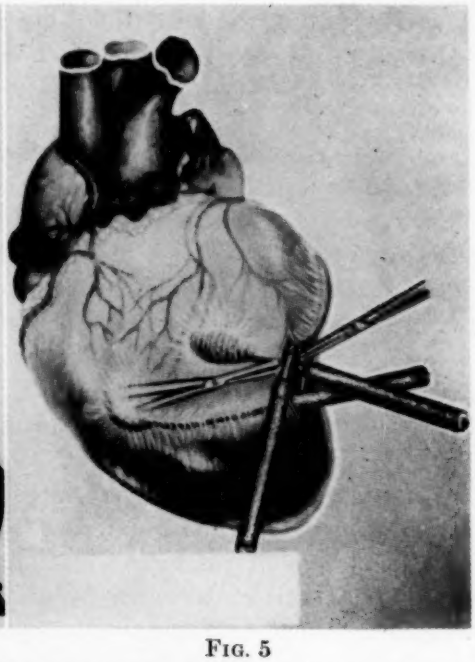

FIG. 5

FIG. 4. Incision of pericardium after lifting it away from myocardium with curved needle.
FIG. 5. Scarification of pericardium and epicardium with Beck burrs.

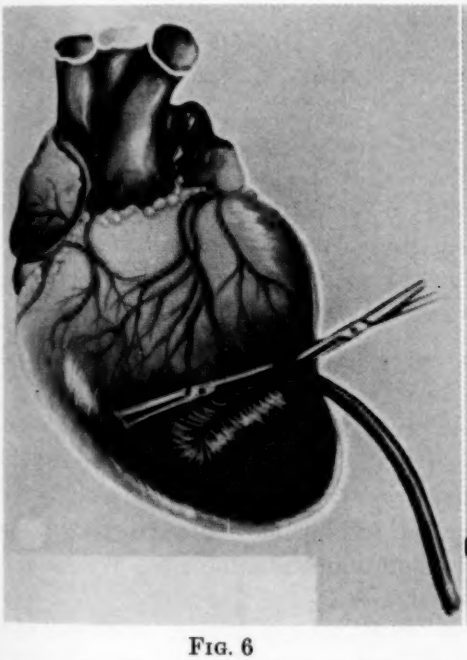

FIG. 6

FIG. 7

FIG. 6. Removal of fluid from pericardial sac by suction through catheter.
FIG. 7. Insufflation of magnesium silicate into pericardial sac by specially designed atomizers.

The condition of the heart following surgery, from the immediate postoperative period up to six years later, is shown diagrammatically in Figure 8.

Indications

We wish to emphasize that although cardiopexy is not to be considered a universal panacea for all types of coronary heart disease, nor a substitute for competent medical management, our results have been most gratifying in properly selected patients.

There must be a definite diagnosis of coronary heart disease. In the following types of cases, relief, protection and considerable benefit may be expected:

1. Angina of six months' duration or longer that is not controlled by medical therapy.
2. Coronary insufficiency in patients aged 30–40, who suffer from angina without myocardial infarction.
3. Coronary heart disease associated with 1 or more infarcts but no severe muscle damage, in patients suffering from dyspnea and angina, who fulfill our surgical requirements, namely a) a lapse of four to six months since the last myocardial infarction; b) cardiac stability, demonstrated by the findings in 3 electrocardiograms, by normal sedimentation rates and white blood cell counts (on 3 alternate days) and by normal serum transaminase activity; and c) the results of "C" reactive protein tests to rule out rheumatic activity.

Contraindications

1. Congestive failure.
2. Active or recent myocardial infarction or occlusion. This precludes operation for a period of four to six months.
3. Severe liver or kidney damage which will impede recovery.
4. Advanced age—over 70 years.

Hypertension is not a contraindication to our operative procedure. Many patients who are adjusted on a compensatory basis have been considerably improved.

RESULTS

The results in our series of 78 patients (10 women and 68 men) after six years of observation, were as follows:

1. There were 3 surgical deaths; 2 occurred about four to five hours after operation, and 1 occurred after five days, from acute infarction as confirmed by autopsy reports. All these deaths were in our early series. We believe they were precipitated largely by the Master's exercise test, which we have discontinued except as a diagnostic measure in an occasional questionable case. We have not had a surgical death in our last 48 operations.
2. All patients returned to work, except 3 who retired as they were well along in years.
3. All except 3 discontinued the use of drugs. Two of these 3 had periods of congestive failure and severe muscle damage at the time of surgery, but no longer require medication for angina. The third patient has occasional anginal pain on exertion.

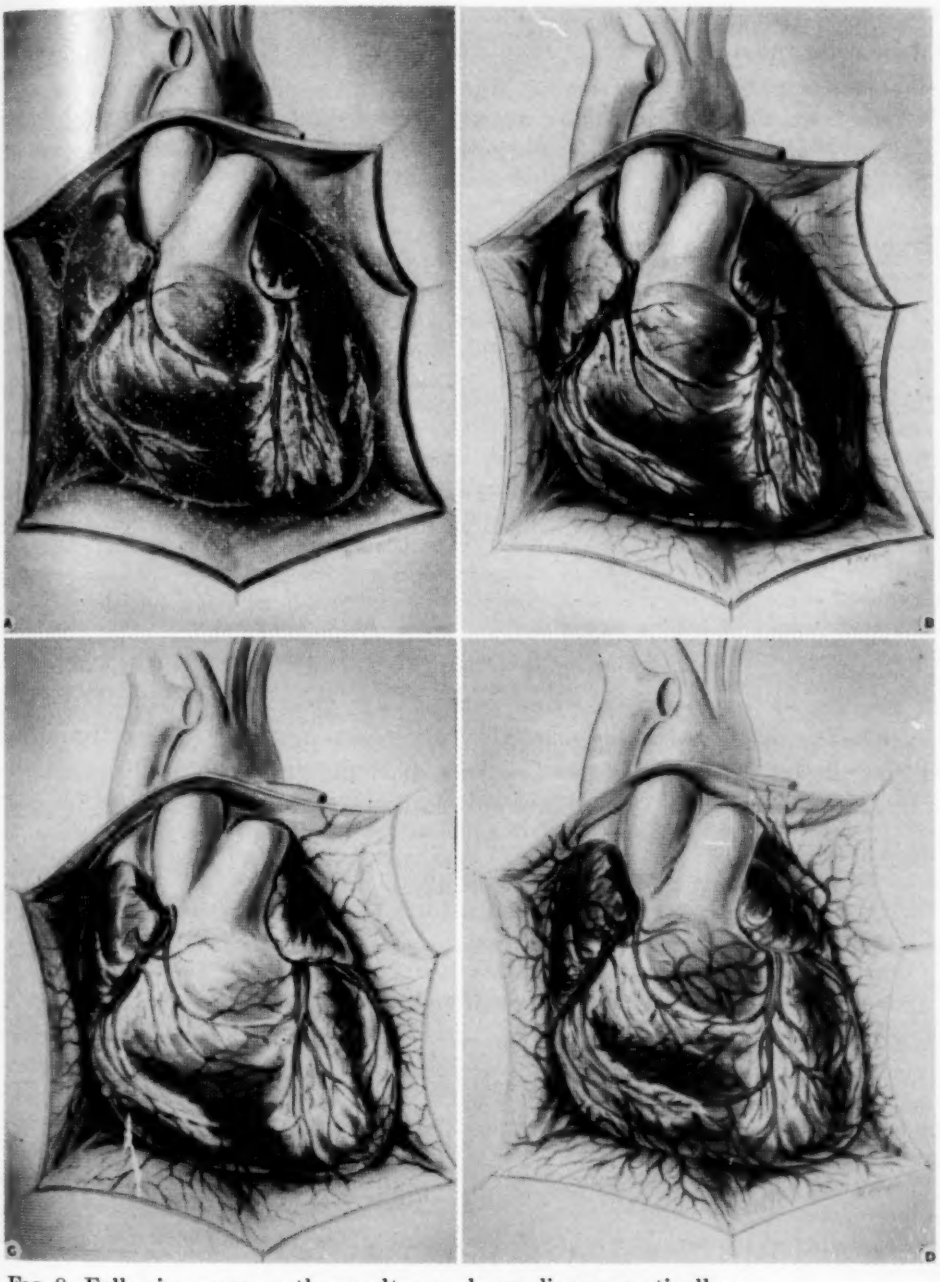

FIG. 8. Following surgery, the results are shown diagrammatically:

A. At 48 to 72 hours.
B. At 6 to 8 weeks.
C. At 1½ years.
D. At 6 years.

4. All patients showed an increase in exercise tolerance.
5. Eight patients have had recurrent attacks, with recovery.

Cardiopexy should be performed before the patient's heart is badly crippled by the disease. Both the layman and the profession should conquer their fear

of cardiac surgery, as by this simple surgical technique we can accomplish in an hour what the myocardium attempts to do in weeks, months or years, perhaps without success.

It is not the occasional patient who survives frequent coronary attacks over a period of years that concerns us here, but the great number that are lost under medical therapy alone.

Proof of benefit in the laboratory animal:

1. Reduction in mortality.
2. Reduction in size of infarcts following ligation of a major coronary artery.
3. Prevention of death of muscle beyond the point of occlusion.
4. Uniform distribution of blood and oxygen, by intercoronary and extracoronary connections.
5. An increase in the intercoronary flow of blood amounting to 5 cc. per minute, as shown by the Mautz-Gregg backflow test (12).
6. Prevention of ventricular fibrillation and death in the majority of revascularized animals.

Proof of benefit in the human subject:

1. Most important—reduction in mortality.
2. Reduction in morbidity. Most patients are greatly improved physically. They become useful members of society again and return to work. Emotional and mental equilibrium is restored and the patients gratefully realize that they are more fortunate than the majority of cardiac cripples unaware of the possibilities of surgical therapy.
3. The impressive list of patients who have been thus protected (contrasted with the few who recover by medical means alone) and their consistently increased life span.

Case Reports

A. K. was a 61-year-old woman who had severe pain in the left chest and was unable to walk or work without having to take nitroglycerin and other vasodilators. Electrocardiograms were abnormal. The electrocardiographic changes were consistent with coronary insufficiency on the basis of coronary heart disease with posterior-wall myocardial inarction.

The patient underwent operation on July 3, 1954, by our cardiopexy procedure. Recovery was uneventful. She returned to work as a parole officer and could walk and climb stairs without pain or shortness of breath. She has been examined periodically during the past three and a half years, and there has been no return of symptoms.

J. K. was a 43-year-old man who had had an acute myocardial infarction on January 23, 1955. He was hospitalized for one month. Since then he had chest pains, especially after walking only a block in cold weather, or on climbing stairs. Electrocardiograms were abnormal and indicated coronary insufficiency. The ST segment was depressed, with evidence of old postero-lateral infarction.

Cardiopexy and ligation of both internal mammary arteries was performed on April 3, 1957. The patient was discharged from the hospital ten days later, free from pain and distress. The pulse rate was 72. Two weeks after operation, the patient walked one and a half miles. He returned to work one month postoperatively and has had no symptoms of angina. He states that he has improved 100 per cent.

C. H., a 52-year-old man, had experienced 4 heart attacks with severe pain in the chest, nausea and vomiting. He was unable to walk more than half a block without severe pain. Pain and distress were almost constant, without nitroglycerin. Electrocardiograms were abnormal, showing evidence of cardiac ischemia. Mild diabetes was controlled with Orinase.

Cardiopexy and ligation of both internal mammary arteries was performed on June 15, 1957. The patient was discharged from the hospital nine days later, in an improved condition. He returned to work on July 29. On August 1, 1957, his condition was good. He was working and could climb stairs and walk considerable distances without pain.

C. L., a 62-year old man, was first seen on November 8, 1957. A complete history was available for a period of seven years. Since this record is a typical one in most respects for the majority of patients with coronary insufficiency and angina, it is presented in detail.

Seven years before, he had consulted an internist. His complaints had been gasping, and a feeling that his heart "turned in the chest" and that his pulse stopped and missed beats. He was treated with quinidine for extrasystoles without improvement. Thiamin hydrochloride (50 mg. per day) relieved the symptoms, and after about four months, extrasystoles ceased. Several electrocardiograms revealed a right bundle branch block and inverted T waves. These findings did not change until he was operated upon, despite severe aggravation of his subjective symptoms. There was gradual development of angina which began about two and a half years before he was seen here.

Anginal pain began mildly under emotional stress or sexual activity, and was relieved by rest and cessation of physical exertion. Two months later, nitroglycerin was needed to relieve the pain in the left shoulder and arm and the numbness in the fourth and fifth fingers of the left hand. Next, he experienced pain when walking fast, walking slowly carrying a load, or walking after a heavy meal. Long-acting vasodilators were prescribed, but as time went on, symptoms increased in intensity. He was warned by his internist to avoid cold air and exertion, and to take it easy.

The patient became extremely depressed. Although formerly he was active and aggressive, he lost interest in everything. He became so disturbed emotionally that he finally consulted a psychiatrist who prescribed a high-vitamin concentrate, androgen, reserpine, work, activity and rope-jumping. Rope-jumping and activity brought on more severe attacks. He secured work, which was strenuous, and nearly collapsed from several anginal attacks. He stopped working after two weeks. He became very forgetful and more depressed. Then he had a severe attack of prostatitis, and underwent suprapubic prostatectomy, from which he recovered uneventfully. He was awakened from sleep by anginal attacks and obtained relief, with or without nitroglycerin, by sitting up. Remissions occurred for several days during the summer. However, the attacks became more severe and he was unable to walk more than two blocks without pain in the left shoulder and arm and in the middle ear.

Night attacks became more frequent and were associated with hypoxia and cyanosis. The dosage of long-acting vasodilator drugs was doubled, without improvement. Nitroglycerin provided little relief unless he inhaled oxygen, which he kept at the bedside.

He became greatly disturbed and lost all confidence in doctors when his internist told him that he was not certain that he had angina and instructed him to stop the use of nitroglycerin. He was instructed to take two Empirin tablets twice daily and on retiring. This medication did not control the pain. The patient had to take as many as four $\frac{1}{100}$-gr. tablets of nitroglycerin per hour for relief. Night attacks appeared as soon as he lay down, and were relieved only by opiates.

Cardiopexy and ligation of the internal mammary arteries was performed on November 12, 1957. The heart showed many adhesions, scars, and evidence of a previous severe pericarditis. Only the anterior adhesions were removed; bleeding made it unsafe to sever the posterior adhesions.

The patient sat up on the evening of the day of operation and walked around for about ten minutes. He was up and walking, intermittently, for four hours the following day. He complained only of incisional pain; all anginal pains had stopped. He was discharged from the hospital five days after operation. He took Pentritol (2 capsules daily), which he discontinued after twenty days. Two weeks after surgery, he was able to walk briskly for

considerable distances, with minimal discomfort in the chest. After four and a half weeks, he returned to work at his original pace. He became active in writing, lecturing and selling, and his mental and emotional tone returned to former levels. When the temperature dropped to 20°F., he walked outside without discomfort, unaffected by cold winds. He now climbs stairs without difficulty. Several examinations since operation have revealed no abnormal objective findings. From all appearances the patient has recovered fully.

As emphasized previously, the operation which we have described is not to be considered a cure-all for coronary heart disease. We do not propose it as a substitute for medical management. The screening procedure must be executed very carefully. Our patients are advised of the tremendous importance of continuing with their cardiologist, internist or general practitioner. Constant vigilance is necessary, not only for control of the diet, weight, and general condition, but for the purpose of continuing the medical treatment these patients require. Only constant attention by competent physicians can satisfy this need in order *to arrest the disease after the relief of angina and protection of the heart by this surgical procedure.*

With this kind of teamwork between the medical man and the surgeon, many patients who are seemingly lost, can be saved. Prophylactically, by maintaining these patients on a low-cholesterol, low-fat diet (the fats not to exceed 20 per cent of the calories), the mortality from this disease can be reduced greatly.

Bilateral Internal Mammary Artery Ligation

During the past ten months, we have added to our surgical program of cardiopexy, the procedure of bilateral internal mammary artery ligation (13). These vessels are ligated, one on each side of the sternum, at the second intercostal space. This provides relief for patients who do not meet the surgical requirements for cardiopexy, and for those who have had cardiopexy but have obtained only 50 to 75 per cent improvement.

In the latter group were 4 patients who had undergone cardiopexy from eight months to two and a half years previously. They felt the need for additional help, as they had to take nitroglycerin or other vasodilators from time to time, as prescribed by their attending physicians. Following ligation of the internal mammary arteries, there was decided improvement. These patients have been able to dispense with the additional drugs. However, it is too early to determine how long the improvement will last.

This operation has also been performed for relief of: 1) paroxysmal ventricular tachycardia due to coronary heart disease, 2) the shoulder-arm syndrome, 3) angina and substernal distress, and 4) angina and coronary insufficiency in patients who do not fulfill the requirements for cardiopexy.

Since no electrocardiographic changes occur during internal mammary artery ligation, it can be performed two weeks after recovery from the initial shock of an acute infarction. This operation guards against further necrosis, supplies the heart with the additional blood needed for recovery, helps to prevent ventricular fibrillation and relieves angina—thus enhancing recovery while the patients are still undergoing medical therapy. This operation is safe and there should be no mortality.

In our series of 25 patients to date, it has been surprising that so much has been accomplished in the way of relief of symptoms of coronary heart disease by this minor procedure. However, in our experience, the best results are obtained when this operation is combined with cardiopexy; or, if it be performed as a preliminary step, it should be followed by cardiopexy after the electrocardiogram has become stabilized and the patient has met all surgical requirements.

We have performed 5 combined operations, and the relief of symptoms has been dramatic. The end-results can be evaluated only after a period of years, as in the case of other surgical procedures.

Medical Therapy Versus Medical Therapy Plus Surgery

In order to determine the value of our cardiopexy operation clinically, we studied the records of all patients with coronary heart disease who were admitted to the Edgewater Hospital during the period 1952–1957, and who were treated medically. The results of this study are summarized in Table 1.

The total number of patients admitted was 983. Of these, 188 (19 per cent) died before leaving the hospital, and 90 (9 per cent) died after leaving the hospital—a total of 278 deaths, or 28 per cent mortality. Seven hundred and five patients (72 per cent) are still alive. Of the 983 patients, 261 (27 per cent) were receiving Dicumarol therapy. Of the 188 who died in the hospital, 39 (21 per cent) were receiving Dicumarol. The average hospital stay was thirty days.

TABLE 1. *Five-Year Study of Patients Treated Medically for Coronary Heart Disease in Edgewater Hospital*

	1952	*1953*	*1954*	*1955*	*1956*	*Total*
No. of patients admitted to hospital	131	143	170	266	273	983
Died before leaving hospital	29—22%	20—14%	34—20%	59—22%	46—17%	188—19%
Patients admitted who were receiving Dicumarol	36—27%	40—28%	44—26%	59—22%	82—30%	261—27%
Died before leaving hospital (receiving Dicumarol)	6	5	4	13	11	39
Died after leaving hospital	18—14%	20—14%	15—9%	27—10%	10—4%	90—9%
Total deaths	*47—36%*	*40—28%*	*49—29%*	*86—32%*	*56—21%*	*278—28%*
Total living patients	*84—64%*	*103—72%*	*121—71%*	*180—68%*	*217—79%*	*705—72%*
Living hospitalized patients						
With repeated attacks	20 (24%)	28 (27%)	30 (25%)	31 (17%)	21 (10%)	130 (18%)
With repeated attacks (receiving Dicumarol)	4	10	10	7	8	39
With repeated attacks (not receiving Dicumarol)	16	18	20	24	13	91
Living non-hospitalized patients						
With repeated attacks	11 (13%)	12 (12%)	13 (11%)	25 (14%)	20 (9%)	81 (11%)
With repeated attacks (receiving Dicumarol)	6	3	8	8	7	32

TABLE 2. *Medical Therapy versus Medical Therapy plus Surgery*

	1952		1953		1954		1955		1956		Total	
	Med. Rx	Med. Rx + Surg.	Med. Rx	Med. Rx + Surg.	Med. Rx	Med. Rx + Surg.	Med. Rx	Med. Rx + Surg.	Med. Rx	Med. Rx + Surg.	Med. Rx	Med. Rx + Surg.
No. of patients admitted	15		19		17		19		8		78	
Died before leaving hospital	4	0	2	3	4	0	3	0	2	0	15	3
	27%		11%	16%	24%		16%		25%		19%	4%
Died after leaving hospital	5	3	1	3	2	0	3	0	0	1	11	7*
	33%	20%	5%	16%	11%		16%			13%	14%	9%
Total deaths	9	3	3	6	6	0	6	0	2	1	26	10*
	60%	20%	16%	32%	35%		32%		25%	13%	33%	13%
Total living patients	6	12	16	13	11	17	13	19	6	7	52	68
	40%	80%	84%	68%	65%	100%	68%	100%	75%	87%	67%	87%
Average hospital stay (days)	31	12	35	11	36	13	23	12	23	11	29.6	11.8

* Our surgical statistics include 2 late deaths from causes unrelated to the disease (1 from abdominal aneurysm and 1 from accident). If these were eliminated, the mortality in our entire series would be reduced from 13% to 10%, and the survival rate increased from 87% to 90%.

The mortality rate for this group should not be confused with the overall mortality rate for coronary heart disease, which is considerably greater, since many patients die without being hospitalized.

We realize the difficulty in making a comparison to determine the value of our surgical procedure. However, as representative surgical candidates for comparison, we took at random 78 medical patients admitted to the hospital during a five-year period, who had suffered from angina pectoris or from one or more myocardial infarcts at least six months prior to admission. The results of our study are summarized in Table 2.

Of the 78 patients, 15 (19 per cent) who were treated medically died in the hospital, whereas only 3 (4 per cent) of those treated surgically (early series) died. Eleven (14 per cent) of the medical group died after leaving the hospital; in the surgical series there were 7 deaths (9 per cent) after discharge. Total deaths in the medically treated group were 26 (33 per cent); and in the surgically treated group, 10 (13 per cent). Of the patients under medical management, 52 (67 per cent) are still living; of those treated surgically, 68 (87 per cent) have survived.

As noted in Table 2, if we were to exclude 2 late deaths from causes unrelated to coronary disease, the total mortality rate in our surgical series would be reduced to 10 per cent, and the survival rate would be increased to 90 per cent.

Morbidity: Surgically treated patients were able to leave the hospital within twelve days on the average, whereas under medical therapy the average stay was thirty days.

SUMMARY

During the past six years, we have operated upon 108 patients with coronary heart disease, to relieve either angina pectoris or coronary insufficiency associated with one or more infarcts. These operations were as follows:

40 cardiopexy operations by the Thompson technique.
38 cardiopexy operations by the Mazel modification of the Thompson-Beck procedures.
25 bilateral internal mammary artery ligations.
5 combined internal mammary artery ligations and cardiopexy.

Results have been excellent with regard to 1) increase in life span, 2) relief of angina, 3) increase in exercise tolerance, 4) ability to return to work, 5) reduction in length of hospital stay, 6) reduction in, or complete elimination of, the use of drugs, and 7) reduction in the mortality rate as compared with that in a similar series of medically treated patients, namely 13 per cent versus 28 per cent.

The addition of bilateral internal mammary artery ligation to our surgical program, has provided a means of immediate relief in certain cases of angina pectoris and coronary insufficiency. By ligating these arteries two to three weeks following an acute myocardial infarction, recovery is enhanced while patients are still under medical management. The operation also affords relief to certain patients who do not qualify as candidates for cardiopexy. We have no assurance, however, that it will provide the same protection as that which follows cardiopexy.

There has been no surgical mortality in our entire series of internal mammary artery operations, probably because we have always waited several weeks after an acute attack before ligating these vessels. This allows the heart to become stabilized. In our early work with cardiopexy, we experienced the same surgical mortality difficulties when we operated too soon. In our last 53 cardiopexy operations (including the combined procedure) there has been no surgical mortality and only 1 late death.

With the present combines surgical procedures, patients can be given relief. They can be restored to society and can return to work within a month after operation.

In our opinion, the operation is safer than the disease. Beneficial results obtainable by medical measures alone can be augmented by cardiopexy and bilateral internal mammary artery ligation.

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EMERGENCY SURGERY IN THE ELDERLY PATIENT

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The reluctance of the physician in recommending surgery to the elderly patient has still not been overcome sufficiently to offer all the benefits which progress in geriatric surgical management has taught us.

In recent years there has been an increasing number of articles pertaining to surgery in the elderly patient. These reports have shown that greatly improved methods of treatment, and consequent decreased mortality, now afford the elderly patient a surgical prognosis which is favorably comparable with that in younger age groups (1–7). The improvement in morbidity and mortality is the result of better evaluation of the patient's physiologic reserve, and thus more accurate preparation for surgery. At the same time there have been great strides in the perfecting of surgical techniques and anesthesia, and in the prevention of infection.

In spite of the proven merits of the new methods, re-orientation of medical attitudes takes time. Habits are difficult to change, especially those rooted in a conservative tradition and strengthened by longstanding experience. Reservation still exists when the elderly patient shows indications of requiring emergency surgery. In this eventuality delay is often postulated in the vain hope that time may render surgery unnecessary.

This article confines itself to the problem of emergency surgery in the elderly patient. It presents evidence that advanced age should not be a contra-indication for surgery, and that prompt and accurate management and early surgical intervention provide the best results.

ANALYSIS OF MATERIAL

During the two-year period 1954 and 1955, 1,267 patients over the age of 65 were admitted to the general surgical wards at Cook County Hospital. (This number does not include traumatic, orthopedic or neuro-surgical admissions). Of these cases, 169 or 13.3 per cent were surgical emergencies.

Table 1 shows the sex distribution of the patients, and their age in five-year groupings.

In Table 2 the details of diagnosis, type of operation, and mortality rate are listed. Of the 169 emergency patients, 128 were operated on within six hours of admission to the surgical service, and none later than twenty-four hours. There was 1 exception—a patient with a bleeding gastric ulcer who subsequently died. Thirty-three patients (20 per cent) underwent additional surgical procedures subsequent to the emergency operation.

TABLE 1. *Sex Distribution and Age in Five-Year Groupings of 169 Emergency Surgical Patients*

Age (yrs.)	Male	Female	Total
65–69	41	16	57
70–74	40	20	60
75–79	19	14	33
80–84	5	8	13
85–89	3	2	5
over 90	1	—	1
Totals	109	60	169

TABLE 2. *Diagnosis, Surgical Procedure and Operative Mortality*

Diagnosis	Operation	No. of Patients	No. of Deaths
Strangulated inguinal hernia	Herniorraphy	30	
	Herniorraphy & small bowel resection	12	2
Strangulated femoral hernia	Herniorraphy	7	
	Herniorraphy & small bowel resection	3	1
Strangulated incisional hernia	Mayo type repair	2	
Acute appendicitis	Appendectomy	25	1
Acute cholecystitis	Cholecystectomy	2	
	Cholecystotomy	3	
Perforated duodenal ulcer	Repair	8	
Perforated gastric ulcer	Repair	4	1
Bleeding duodenal ulcer	Gastrectomy	13	2
Bleeding gastric ulcer	Gastrectomy	5	1
Intestinal obstruction resulting from carcinoma of the large bowel	Colostomy	18	3
Diverticulitis	Colostomy	3	
Intestinal obstruction resulting from adhesions	Lysis	11	1
	Lysis and bowel resection	4	1
Regional ileitis	Iliotransverse colostomy	1	
Volvulus of the sigmoid	Resection of the nonviable bowel and end-to-end anastomosis	2	
Prostatic hypertrophy	Suprapubic cystotomy	14	2
	Prostatectomy	1	
Perinephric abscess	Incision & drainage	1	
Total		*169*	*15 (8.8%)*

Pathologic findings

The conditions necessitating emergency surgery fell into 4 large categories, namely, acute abdominal disorders, strangulated hernias, gastro-intestinal bleeding, and acute urinary retention (for details see Table 2). Acute abdominal conditions constituted the largest group—81 cases. The causes were intestinal obstruction resulting from neoplasm, adhesions, volvulus of the gut, and regional

ileitis. Other underlying disorders included acute appendicitis, perforated peptic ulcer, acute cholecystitis and diverticulitis.

There were 54 strangulated hernias, of which 15 required bowel resection. Eighteen patients underwent gastrectomy for bleeding peptic ulcer, and 15 were treated for acute urinary retention. In 1 patient a left perinephric abscess was incised and drained.

Unrelated pathologic conditions

As is common with advancing age, many of the patients on admission had pathologic lesions not directly associated with the chief complaint (Table 3). These conditions had to be taken into account, both in the plan for surgery, and the pre- and postoperative management.

Seventeen of the patients had a history of previous heart attacks, and 30 had abnormal electrocardiographic findings. Three patients were receiving digitalis at the time of admission to the hospital; an additional 10 had to be digitalized rapidly prior to surgery; and 2 were digitalized during the postoperative period. Thirteen patients had longstanding hypertension with a blood pressure over 180/100, and 7 had diabetes—well controlled.

None of the foregoing patients experienced any unusual difficulties during surgery or postoperatively.

Anesthesia

In 67 patients the anesthesia was general; in 73, local; and in 29, spinal. All of the surgical procedures, except bowel or gastric resections, took less than an hour to perform.

Morbidity and mortality

The incidence of postoperative complications was surprisingly low. There were 4 cases of pulmonary infection; only 1 of thrombophlebitis; 2 cases of cardiac

TABLE 3. *Unrelated Pathologic Conditions*

Complaint	No. of Patients
Generalized arteriosclerosis (positive retinal findings but E.K.G. normal)	27
Myocardial damage; infarcts; coronary insufficiency; or occlusion (proved on E.K.G.)	30
Auricular fibrillation	2
Complete A.V. block	3
Bundle-branch block	1
Hypertension (minimum, 180/100)	13
Emphysema with asthmatic manifestations	7
Diabetes	7
Parkinsonism	2
Hemiplegia resulting from cerebrovascular accident	3
Prostatic hypertrophy with urinary retention over 25 cc	9
Peptic ulcer	2
Pulmonary tuberculosis	1
Pernicious anemia	1
Chronic lymphatic leukemia	1

decompensation (1 death); and 3 of urinary infection. During the first postoperative week, symptoms and signs of acute gastric ulcer (proved by x-ray examination) developed in 2 patients who previously had experienced no difficulties of this sort.

Table 4 shows the number of deaths and the causes. Included are all patients who died prior to leaving the hospital, or before a second surgical procedure had been completed.

Six deaths were attributed to cardiovascular disorders. Two were due to myocardial infarction (1 on the third and 1 on the sixteenth postoperative day); 1 to cardiovascular collapse within the first twenty-four hours after surgery; and 1 to mesenteric thrombosis on the second postoperative day. Another death was due to a cerebrovascular accident on the fifth postoperative day, in a patient who had a blood pressure of 170/95 prior to the operation (for acute appendicitis) but, except for a moderate degree of arteriosclerosis, had no other apparent difficulties. The sixth patient died on the operating table from general cardiovascular collapse. Out of a total of 1,267 patients operated upon during the two-year period under consideration, this was the only death to take place under these circumstances. This man had a bleeding duodenal ulcer, was admitted to the hospital on November 8, and underwent operation on November 10. During the intervening two days he had 4 large hematemeses and received 7,500 cc. of blood. The anesthesia was of the continuous spinal type. In retrospect, it is felt that surgery was delayed too long, and that the outcome might perhaps have been better with the use of a general anesthetic and muscle relaxants.

Three patients died from what was diagnosed as overhydration after surgery. Postoperatively, 2 of these patients received 6,000 cc. of fluid during the first forty-eight hours, and 1 received 7,500 cc. during the first sixty hours. Pulmonary edema developed in all 3, in spite of apparently normal cardiovascular and pulmonary reserves. The fluid and electrolyte replacement in each case was carefully estimated on the basis of the daily need indicated by the results of blood chemical determinations, intake and output charts, and the general physical condition of the patient.

Three patients died from pneumonia, 2 from carcinomatosis, and 1 from pulmonary embolism on the fourth postoperative day.

It is noteworthy that all of the 19 patients over the age of 80 survived. In only 1 of them did a postoperative complication (pneumonia) develop. The average

TABLE 4. *Causes of Postoperative Death*

Cause of Death	No. of Patients
Cardiovascular	6
Overhydration	3
Pneumonia	3
Carcinomatosis	2
Pulmonary embolus	1
Total	15

stay in hospital of the octogenarians was 9.9 per cent longer than that of patients under the age of 65.

Comparative statistics

In reviewing any large series of cases, statistical comparison with other reports is not only difficult but often misleading. The great number of variables such as type of patient, diagnosis, associated pathologic conditions, and choice of anesthetic render comparison legitimate in only the broadest of terms. According to current reports (8–10) the average mortality rate for elective surgery in patients over 65 years of age is between 5 and 6 per cent; for emergency surgery, it is between 15 and 20 per cent. The figures from Cook County Hospital are 4.9 per cent for elective surgery and 8.8 per cent for emergency surgery in 1,267 patients operated on over a two-year period. These results are all the more remarkable when it is considered that Cook County Hospital is a charitable institution, and that many of the patients admitted to the hospital are in a markedly debilitated condition resulting from their poor environment, low economic status, and educational limitations.

GENERAL CONSIDERATIONS AND DISCUSSION

Within the last fifty years the average life expectancy in the United States has increased by twenty years—from age 48 to age 68. By the year 2,000 one can optimistically expect to live eight decades. With increasing longevity surgeons are being confronted with ever-growing numbers of patients whose mere age, only a few years ago, was considered a contra-indication for surgery.

Nevertheless, in treating the elderly person, the surgeon should take greater cognizance of the patient's physiologic rather than chronologic age. The fact that the patient is advanced in years should not, in itself, classify him as a greater surgical risk. However, it does necessitate a more astute evaluation of his general body functions and potential physiologic reserve.

With the passage of years the structures and processes of the body deteriorate and become less efficient. In addition to a decreased basal metabolic rate, the elderly patient usually exhibits reduced reserves and incompetent function in some or all of the vital organs.

Importance of early intervention

In elective surgery, lengthy preoperative treatment is usually of great benefit to the patient. It provides him with a solid therapeutic foundation upon which he can draw for extra resistance to meet the demands which surgical trauma imposes upon the system.

In contrast, emergency surgery affords no such comforting bulwark. Because of the elderly patient's decreased physiologic reserves and inability to tolerate prolonged stress, he requires preoperative treatment which will give him the maximum benefit in the shortest time. Speed is of the essence—in the decision to operate, in the preparation, and in the operation itself.

Although a reasonable delay for the preparation of the patient is not only

necessary, but beneficial, the elderly patient undergoing an emergency procedure requires astute and accurate judgment of the time factor if good results are to be expected. Preoperative treatment, whenever possible, should be completed within the shortest time after admission to the hospital. Operation should be performed when the patient is judged to have attained the optimal benefit from the preparation. It is the authors' experience that if preoperative treatment is continued for much longer than six hours, deterioration in the general condition starts to undermine the benefits of this preparation, and the patient begins to lose ground.

When symptoms and signs indicate that the condition is of an emergency nature, no time should be wasted in the decision to operate. "Let's see the patient again in a few hours, and then we'll decide," is an attitude which too often has led to fatal results.

Preoperative management

Preparation of these patients should start even before the decision to operate has been made. Preoperative management consists of evaluation of the patient's physical state and physiologic reserve, and the selection of the treatment required to correct whatever deficiencies are manifest.

Many patients admitted for emergency surgery require blood and/or fluid and electrolyte replacement. Calculation of the amounts to be administered should not be based solely on laboratory findings (such as blood volume, plasma electrolyte levels, hematocrit readings, and CO_2 combining power). The capacity of the patient's cardiovascular system and other vital organs for handling a sudden increase in intravascular volume, must also be taken into account. As it is not possible to estimate exact tolerance to the intravenous administration of fluids, corrective management should tend towards underhydration.

Blood volume should be estimated prior to surgery, as many elderly patients have a normal blood count and hematocrit reading in asso iation with a reduced volume of circulating blood. The quantity of blood replacement in such cases should be estimated on the basis of the ideal weight of the patient, and not on his weight at the time of admission to the hospital (11, 12). In all the patients of this series, electrocardiograms and chest roentgenograms were obtained before surgery. In 34, distinct cardiac abnormalities were evident. Nine of these patients gave histories of cardiac infarction or coronary thrombosis of at least one year's duration prior to the current surgical complaint. This group underwent operation without difficulty, and it would appear that the foregoing defects (provided they are not of recent origin) need not be deterrents to surgery.

Similarly, concurrent conditions such as hypertension and diabetes were found not to increase the surgical hazards or postoperative complications, as long as they are well controlled.

The prediction of possible cardiac decompensation and the preoperative evaluation of cardiac reserve are often very difficult. Of the 169 patients, 10 were digitalized prior to surgery. Six of these showed definite signs of vascular congestion, and 4 had no apparent history of decompensation or cardiac failure. More careful enquiry, however, revealed that they experienced mild dyspnea on exertion, and that their circulation time was prolonged.

Routine digitalization of elderly patients is not advocated. Nevertheless, when in doubt as to the cardiac reserve, it is well to remember that tolerance to major surgery is apparently increased when the patient is digitalized. There can be no hard and fast rule in this matter, but experience in handling geriatric patients will put the surgeon on his guard, particularly with those patients whose tolerance to exercise is reduced because of advanced age, or whose mobility is minimal due to chronic disease or other physical causes.

The limited time available for an emergency operation permits only a simple examination of the urine. No renal or hepatic function tests can be performed. The physiologic reserve of these organs must, therefore, be evaluated mainly from the patient's history. If there is any urinary retention, a retention catheter should be inserted and kept in during operation and the immediate postoperative period—or even longer, if required, especially in the presence of prostatic hypertrophy.

Pulmonary reserve can usually be estimated fairly accurately. This is particularly important in relation to the selection of the anesthetic.

Emergency surgical patients should be moved as little as possible. The taking of the history and physical examination by 2 interns, 3 residents, 5 students and a couple of consulting surgeons should be avoided. Prior to surgery, the patient should not be moved unnecessarily from stretcher to bed, to x-ray room, and vice versa. When x-ray films are required, they should be obtained at the bedside.

The psychologic outlook of the elderly patient is important. The necessity for undergoing surgery, particularly when advanced in years, creates understandable depression and resignation to death. Although an elderly person may entertain the possibility of the termination of his existence with more calm than a younger person, this attitude in itself weakens his desire to survive. Loneliness, lack of affection, inhospitable social circumstances and prolonged ill-health are just a few of the factors which may appear to the elderly patient to constitute sufficient reason for succumbing to his illness. A solicitous and encouraging physician can contribute immeasurably to the confidence and buoyancy of a patient's spirits. In spite of the power of medical science, its efficacy can be greatly impaired and even nullified in the battle between a fighting body and a prematurely defeated mind. Even though the realm of the body is the physician's prime concern, he should remember that the amount of good he can do will be determined ultimately by whether his patient is happy, assured and cooperative, or listless and indifferent.

Choice of anesthetic

While preparation for surgery is being carried out it is desirable that the anesthetist be called in personally to evaluate the patient with the surgeon. Although final choice of the anesthetic usually lies with the anesthetist, the surgeon should, in turn, tell him the plan of surgery and the approximate time required.

The selection of the anesthetic should be based on the appraisal of the disturbed physiologic processes and the amount of pulmonary and cardiovascular

reserve. The anesthetic should not contribute to the aggravation of the patient's already precarious condition.

With decreased cardiac reserve and the loss of venous tone and decreased elasticity of the arteries, the elderly patient has great difficulty in adjusting to rapid changes in circulating blood volume. During all general anesthesia there is a marked increase in peripheral blood flow, and a decrease in the blood flow through the vital organs. This factor should be kept in mind, as even with adequate oxygenation during anesthesia, this redistribution of blood and alteration in blood volume may prove too much for an already tired body.

There is little doubt that in geriatric surgery, particularly in the poor-risk patient, the best results are obtained when a local anesthetic is used. It should be selected, not only when it is the obvious choice, but in every possible instance. When local anesthesia is not practical, spinal anesthesia should be considered. This method does not depress the respiratory centers, and fluctuations in blood pressure can be controlled by ephedrine. When a general anesthetic is selected, it should be used in conjunction with muscle relaxants. This permits a reduction in the amount of anesthetic used.

Surgery

Although the survival of the patient depends predominantly on accurate timing and the method of preoperative management, the speed of the surgical procedure determines to a great extent the degree of trauma inflicted upon the patient.

It is desirable that emergency surgery be brief and limited, and that a measure of individual variation be applied to standard surgical procedures in accordance with the patient under consideration. Often it will be necessary to remove only the immediate cause of trouble, and plan the curative operation for a later date. The elderly patient with his decreased reserves shows poor tolerance to long procedures. With few exceptions, operations which extend much over two hours are either unnecessary or incompetently performed. The records seem to indicate that both increased morbidity and increased mortality are associated with lengthy surgical procedures.

Replacement of blood during surgery should be prompt and adequate. The elderly patient cannot withstand excessive loss of blood, or anoxia.

Postoperative care

The care of postoperative patients in a recovery room has been the practice at Cook County Hospital since before the turn of the century. The recovery room staff is especially trained to deal with the problems of the postoperative period. This is of particular advantage to the elderly patient, whose condition is more prone to sudden unfavorable changes. The recovery room is now an accepted part of postoperative management in many hospitals, and its benefits are clearly manifest in the high percentage of uncomplicated convalescences.

After operation it is preferable that the patient who has had a general anesthetic should not be moved from the operating table until conscious. He should then be placed directly in his bed and wheeled to the recovery room.

Fluid and electrolyte replacement after surgery should be conservative. In the elderly patient there is usually a high retention of salt and fluid until the second postoperative day. This factor, together with inefficient kidneys and inadequate pulmonary and cardiovascular reserves, renders the patient susceptible to oliguria and impairs his ability to secrete and concentrate urine. Within the first twenty-four to thirty-six hours after operation, no more than 2,000 cc. of fluid should be administered, and no salt should be given unless strictly necessary. After the immediate postoperative period, the urinary output of patients with normal renal function is a good index of the adequacy of their fluid intake.

Postoperative breathing exercises should be performed often and regularly. The patient should be made to take a dozen deep breaths every hour, and to move his arms so as to increase the expansion of the thoracic cage.

The patient should be encouraged to cough. If he has difficulty in bringing up sputum because of pain, a nurse or intern should support the wound in such a manner as to facilitate coughing. If atelectasis develops due to a plug, bronchoscopy should be performed. If there is no actual obstruction, but sputum is heavy and the patient has difficulty expectorating, a catheter should be inserted, preferably through the nose. This usually provides relief, but if not, a tracheotomy should be performed without hesitation so that there can be proper aspiration.

The elderly person usually requires smaller doses of medication than a younger one, because of decreased basal metabolism and reduced body functions. Opiates should be administered sparingly so as not to decrease these functions further.

Early ambulation after surgery is desirable. Our patients were encouraged to sit up on the day after operation, and to get out of bed on the second day. If a patient cannot get out of bed he should be moved often, and assisted in exercising his limbs, *e.g.*, simulating the leg movements of bicycle riding lying flat on the back. This may be difficult with elderly persons, but they should be encouraged in every way. If enough time is spent with them they usually cooperate. That early ambulation pays dividends is clearly borne out by the low incidence of postoperative complications, as enumerated under Analysis of Material.

The nationwide shortage of nurses has indirectly resulted at Cook County Hospital in placing upon the patients some of the responsibility for their postoperative care. On returning to the surgical ward from the recovery room, the patient is instructed and encouraged to care for himself as early as possible. Bathing and feeding himself, and even helping other patients, requires direct participation in his recovery and contributes to self-reliance and general mobility, besides constituting an extremely beneficial self-imposed occupational therapy.

SUMMARY

Of the 1,267 patients over the age of 65 admitted to the general surgical wards of Cook County Hospital during the two-year period 1954–1955, 169 required emergency operations.

These 169 cases are reviewed with reference to diagnosis, preoperative, operative and postoperative management, and the incidence of unrelated pathologic conditions.

Mortality for emergency surgery was 8.8 per cent as compared with 4.9 per cent for elective procedures.

These results compare favorably with those in younger age groups, and are discussed in the light of the elderly patient's reduced physiologic reserve and malfunctioning vital organs.

Good results in emergency geriatric surgery depend upon: 1) prompt decision to operate; 2) rapid and brief preoperative preparation; 3) restriction of surgery to removal of the immediate cause of illness; and 4) careful postoperative care with particular emphasis on conservative fluid intake, breathing exercises, early ambulation and the encouragement of self-reliance.

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SELF-GOVERNMENT FOR PATIENTS ON A GERIATRIC SERVICE*

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One of the growing realizations among both professional and lay persons in recent years has been the increase in the aged segment of our population. This increase has demonstrated itself not only in communities across the country but also in our institutions. Recent surveys (1, 2), for example, have shown that by 1960 two-thirds of the patient population in neuropsychiatric hospitals will consist of elderly psychotics. This realization has led to demands for new techniques to meet the special problems posed by this group of patients. However, the enormity of the task, in addition to certain popular misconceptions, has made geriatrics a rather uninviting field of inquiry as well as practice. Thus progress in the area has been slow and lacking in interest.

One of the greatest obstacles encountered in working with most elderly psychotics is the difficulty in communicating with them. Presumably because of their intellectual deterioration and/or psychopathologic condition, attempts to establish contact with them by means of the use of logic or rational methods usually meet with failure. Ginzberg (3), recognizing this difficulty, recommends that the elderly psychotic be approached on an emotional level, appealing to and capitalizing on his excessive needs for appreciation, acceptance and respect rather than relying on the processes of thinking, understanding and verbalization. Ginzberg argues further that, despite the patient's deterioration and confusion, there still exists a powerful motivation for group identification and belongingness, *i.e.*, a desire to be as others are. Gilbert (4) makes much the same point in stating that the important parts of psychotherapy for older psychotic patients are support, reassurance and acceptance in a manipulated environment rather than face-to-face contacts designed to resolve specific conflicts.

The implication in these viewpoints is that the inaccessibility of the elderly psychotic is more apparent than real and that, to a large extent, it is based upon the restrictions set by the patient's social and cultural environment rather than inevitable organic deterioration or decay of function. If this be the case, one could expect that the intellectual capacity of the patient may be realized and utilized in an emotional atmosphere which provides a feeling of security, belongingness, prestige and authority.

Based on this orientation, a program for patient self-government was estab-

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lished on the geriatric service of this hospital in May 1955. It was felt that, with this technique, the patient's preserved tendency toward group identification could well be utilized and that intellectual activity could eventually be stimulated through this medium. The historical development and current status of the program will be briefly outlined.

SELF-GOVERNMENT PROGRAM

The geriatric service of the Tomah Veterans Administration Hospital is a 328-bed unit of an 1176-bed neuropsychiatric hospital. There are approximately 164 patients on each of 2 buildings. Each building is divided into 4 wards with approximately 40 patients on each ward. At the present time 6 of the 8 wards are "open"—that is, all patients on these 6 wards enjoy ground privileges. The majority of patients are chronic psychotics over 60 years of age who had been hospitalized prior to the opening of this hospital in 1947.

Originally, 2 discussion groups (one on each of 2 wards) were organized on an informal basis. The psychiatrist[1] and the clinical psychologist[2] conducted the meetings and initiated the discussions. Nurses and aides also participated. The patients were told at the outset that the meetings were for the purpose of communicating their complaints, suggestions and comments to these representatives of the treatment team. Initially there was little interaction between patients and staff. Most of the patients remained withdrawn and hostile. Gradually, however, they became more responsive. They seemed sincerely to welcome and appreciate the fact that others were willing to listen to their problems and give them some attention. It was not long before interaction occurred and ward problems were more readily communicated. At this point a more democratic spirit emerged. The suggestion was made to elect a leader among the patients, and this was accepted by the group. Later, a secretary was elected by the patients who served with the leader and took minutes at each ward meeting, presenting these minutes to the group for approval at a subsequent meeting.

From this beginning, interest flourished and development of the program progressed rapidly. The current structure is as follows: Patients are organized on each of the 6 open wards. Each ward has its own elected chairman, secretary, and roll-call checker and conducts a weekly half-hour meeting on the ward. Discussion topics are varied, and range all the way from petty grievances to individual plans for leaving the hospital. Three standing committees have been organized. The first is known as the Executive Committee. It consists of all the chairmen and secretaries from the different wards, and has a total membership of 12 patients. The committee meets weekly for one hour preceding the ward meetings, is elected every six months, and has as its principal purpose the planning and coordinating of all activities concerned with the general membership. The second standing committee is designated the Club Committee. It consists

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of 2 elected patients from each open ward, who are rotated on a monthly basis. This Club Committee of 12 patients meets daily with a psychiatric aide and has as its purpose the improvement and maintenance of the Geriatric Club Room. The third standing committee is called the Advisory Committee. Its members are recently retired chairmen and secretaries from the respective wards. This committee functions as an advisory group and counsels newly elected officers on parliamentary procedure. It meets regularly with the Executive Committee. From time to time additional committees are formed as the needs arise. The clinical psychologist and selected nursing personnel meet with the standing committees and with the joint body of patients. They function primarily as liaison personnel between patients and staff.

RESULTS

What are some of the concrete results of this program? First of all, the patients have developed and organized an exclusive club room, which is situated on the geriatric service apart from the wards. Through suggestions made during the ward meetings and with the cooperation of Management and Special Services, they have procured for the club a television set, a radio, a shuffleboard set, soft-drink dispensers, a piano, and a variety of games. The club is nicely furnished and decorated with flowers and pictures. It is operated and maintained by the patients themselves and they take great pride in its existence. The Club Committee is mainly responsible for its cleanliness, but all patients partake in its maintenance and make suggestions for improvements.

Another development of the program is the impetus it has given to ward activity. Weekly, through the ward meetings, patients are assigned to ward housekeeping duties which they are capable of doing, such as making beds, dusting furniture, cleaning floors and rearranging furniture. For the most part, these assignments are volunteered for, and are accepted willingly as a matter of conforming with group wishes. This has had the effect of increasing interaction among patients on the ward, as well as providing purposeful and meaningful activity.

Through their ward meetings and with the help of the Special Services representative, the patients now plan and coordinate their own recreation activities. These include social dances, birthday parties, special musical shows, bingo, and card games. During clement weather, fishing trips, all-day bus excursions, picnics, baseball, and watermelon feasts are planned. Both intra-group and inter-group competitive sports are arranged in pool tournaments, bowling tournaments, and baseball. Thus, activity is not confined within the older age group, but is extended and combined with activity in other parts of the hospital. Decisions relative to the details of the activity are made during the meetings, and patients who indicate a desire to participate are selected in a democratic fashion.

The Executive Committee has drawn up a constitution and set of by-laws to add additional structure to the program. This constitution, among other things, provides a name for the organization, specifies the purposes, and outlines the order of business. The constitution, after having been organized by the Execu-

tive Committee, was printed as a geriatric patient project and then distributed throughout the hospital by the patients themselves. The distribution was made primarily to give additional status to the program.

Experience with this program suggests that it has definite therapeutic value for elderly psychotic patients. In general, the results have been most gratifying in indicating the possibilities of preserving the personalities of even those aged persons who seem badly deteriorated. Probably the greatest value of such a program lies in its potential for restoring to the helpless, defeated and insecure elderly psychotic, feelings of personal worth and adequacy. Through this kind of group activity the patient eventually comes to realize that he is not rejected, but welcomed and accepted by peers with problems similar to his own, as well as by authority figures in the hospital. Self-respect and dignity, profoundly devastated among elderly psychotics, begin to emerge in a new light as the patient finds himself a responsible member of an active committee whose purpose is to help achieve a common goal for the group with which he is already strongly identified. The program encourages active participation in the events of daily life, develops the patient's interest in other persons and things outside of himself, and helps to dispel the feeling of being lonely and isolated. Additionally, such a program provides a direct and convenient channel of communication between patients and staff and often facilitates the solution to administrative problems.

It should be pointed out that the failure or success of such a program depends to a large extent on the close cooperation of, and good interpersonal relationships among the personnel of the hospital. Too often, among hospital personnel there is a general feeling of hopelessness regarding the elderly psychotic, and the attitude that little can be done for him. This attitude, which is easily communicated to the patient, must be modified if success in the program is to be achieved. Furthermore, it seems important that hospital personnel see the merits of such a program, become aware of its role in the total treatment program, and have some idea of the goals to be reached. It has been our experience that these problems can be resolved only through close contact and frequent communication in a team approach.

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ANTIHYPERTENSIVE EFFECTS OF RESERPINE IN SUSTAINED-RELEASE FORM: A COMPARATIVE STUDY

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Therapeutic measures for the treatment of mild or moderate essential hypertension frequently produce side-effects which are more distressing than the symptoms caused by the disease. Obtaining the patient's cooperation, to say nothing of his interest and confidence, is often difficult, and points up the need for antihypertensive drugs that are acceptable to both patient and physician.

One of the most promising antihypertensive drugs developed in recent years is reserpine, an active alkaloid of *Rauwolfia serpentina* (1). Although effective in treating mild and moderate hypertension, reserpine can produce side-effects such as marked depression, undesirable gains in body weight, drowsiness, and nasal stuffiness, all of which limit its utility. Reports also indicate that Rauwolfia drugs can cause exacerbation of ulcer symptoms (2).

Several investigators have reported that the use of reserpine in sustained-release form provides more effective antihypertensive therapy and produces fewer side-effects than does reserpine in tablet form (3–5). This form[1] is designed to provide therapeutic levels of reserpine over a 24-hour period by a slow, continuous release of the drug from specially coated minute pellets. The reports however, do not indicate whether the sustained-release form of reserpine is similarly effective in geriatric patients. The present study was undertaken to compare the antihypertensive effects and the incidence and severity of side-effects produced by reserpine in sustained-release form, in geriatric and in non-geriatric patients.

MATERIAL AND METHOD

Fifty-five patients (22 men, 33 women) were selected for this study. Twenty-eight patients (Group A) were from 19 to 59 years of age, and 27 (Group B) were from 60 to 91 years of age.

Although either a systolic blood pressure over 150 mm. Hg or a diastolic blood pressure over 90 mm. Hg is generally regarded as denoting hypertension (3), only patients with systolic and diastolic blood pressures well above these levels were selected. The average pretreatment blood pressure in Group A was 183/104, and in Group B, 193/104. All measurements were made with the patients in a sitting position. In addition to elevated blood pressure, other symptoms associated with hypertension, such as headache, angina and signs of congestive heart failure were present in most patients. Six patients were classified as grossly obese. Concomitant therapies for conditions other than hypertension were continued; these included hormone preparations, sedatives, analgesics, antibiotics and tranquilizers.

Prior antihypertensive therapy had included Rauwolfia and reserpine in tablet form, and the results had usually been unsatisfactory. The effects of these drugs had varied from time to time and from patient to patient. Moreover, many of the patients had experienced

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[1] Supplied for investigational use as Eskaserp® Spansule® capsules, by Smith, Kline & French Laboratories, Philadelphia, Pa.

disturbing side-effects such as pruritus, depression, drowsiness, nasal stuffiness, gastric distress and dizziness while taking these drugs.

Before therapy with reserpine in sustained-release form was initiated, patients underwent complete physical examinations, and were interviewed to determine their familial, occupational and interpersonal relationships, in order to obtain some idea of their emotional stability. Most of them were tense, nervous people who felt they were under great pressure either in their occupations or at home. Among the male patients were several salesmen, a police officer, a student-athlete, an electrical contractor and several laborers; the majority of the women were housewives. Most of the geriatric patients were retired. During the course of these interviews an attempt was made to help the patients resolve their emotional problems and to work out a program of relaxation, rest and (when needed) diet.

In 49 patients the initial dosage was one 0.50-mg. sustained-release capsule daily. In 6 patients, therapy was initiated with a single dose of reserpine intramuscularly to obtain a rapid antihypertensive effect, and was followed by the usual initial oral dosage of reserpine in sustained-release form. After a week to ten days, dosage was changed to maintenance levels, based on the patient's response to initial therapy. Most patients were maintained on one 0.25-mg. sustained-release capsule once daily. An occasional patient needed 0.25 mg. twice daily or 0.50 mg. once daily. In some instances the dosage schedule was arranged so as to relieve hypertensive attacks during sleeping hours or to accommodate some other individual requirement. Patients were examined at intervals of one to four weeks for periods up to one year.

When the blood pressure became stabilized, or when it appeared that further therapy would not change the symptomatic picture associated with hypertension, an evaluation was made of each patient's response to therapy. This included the amount of reduction in blood pressure, the degree of relief of other hypertensive symptoms, and the incidence and severity of side-effects.

RESULTS

As shown in Table 1, the average systolic blood pressure in the non-geriatric patients (Group A) was reduced by 33 mm. Hg, and the diastolic by 23 mm. In the geriatric patients (Group B) the average reductions were 37 mm. Hg (systolic) and 16 mm. (diastolic). Twenty-one patients (75 per cent) in Group A and 20 patients (82 per cent) in Group B achieved normotensive diastolic blood pressures. Dyspnea, edema, angina and headaches were significantly reduced in 29 patients, and completely relieved in 7.

There was a noticeable diminution of nervousness among the patients, due most probably to the tranquilizing action of reserpine. This was more pronounced in the geriatric group, and may have been related to the fact that symptoms or nervousness and tension were usually less marked among these patients initially.

TABLE 1. *Effect of Sustained-Release Reserpine on Blood Pressure in 55 Hypertensive Patients*

Group	Average Blood Pressure (systolic/diastolic, mm. Hg)			Average Duration of Therapy (months)
	Before Therapy	After Therapy	Reduction	
A. 28 patients, 19–59 years of age.....	183/104	150/81	33/23	9.3
B. 27 patients, 60–91 years of age.....	193/104	156/88	37/16	11.2

The drug appeared to be equally effective in geriatric and non-geriatric patients. Any differences, such as a somewhat greater tranquilizing effect in the older patients, were small enough to be attributable to the sampling factor.

In the 6 grossly obese patients, the systolic blood pressure was significantly lowered. In 5 of them the diastolic blood pressure was also significantly lowered; in 1 it remained unaffected.

There was no significant difference in the incidence of side-effects, between the geriatric and non-geriatric groups. Drowsiness was reported by 6 patients; in 2 it was produced only by the initial dosage and disappeared when the dosage was reduced. One patient reported occasional nasal congestion, and another reported having nightmares. The latter side-effect was associated with the initial dosage, and did not occur with the lower maintenance amounts. In no case were the side-effects severe enough to require discontinuation of the drug.

In 41 of the 55 patients (74.6 per cent) the diastolic blood pressure was reduced to normotensive levels and the systolic blood pressure and other clinical symptoms were significantly reduced without the appearance of undesirable side-effects. These were classified as having had a good response to the therapy. In 7 patients (12.7 per cent) the diastolic blood pressure was significantly reduced, but not to normotensive limits, and there was an amelioration of accompanying symptoms. These were classified as having had a fair response. The remaining 7 patients (12.7 per cent), although benefiting to some degree in several instances, were considered to have had a poor response to the therapy.

DISCUSSION

Although Rauwolfia preparations are reportedly long-acting, it is not uncommon to find patients who experience an uneven effect from these drugs, being more improved at certain times of the day, and less improved at other times. If the drug is given at frequent intervals during the day to overcome this problem, the increased dosage often produces an increased incidence of side-effects, and keeps the patient constantly aware of his condition. The over-all result may lead to an increase in apprehension and a further elevation of blood pressure. The use of reserpine in sustained-release form, on the other hand, reduces the incidence of side-effects and provides more uniform relief of symptoms throughout the day.

Because emotion plays an important role in hypertension, particular attention was paid to any tranquilizing effects the drug might have produced. Mild tranquilization was evident, more so among the older than the younger patients, but no enhancement of symptoms of depression was observed. In this respect also, the sustained-release form in low dosages provides safer therapy in depressed patients than does reserpine in conventional form. In severe cases of hypertension, reserpine in any form would probably not provide adequate therapy. Its moderate antihypertensive and tranquilizing effects might, however, be used advantageously as adjunctive therapy in severe hypertension. It has already been shown, for example, that reserpine permits a reduction in the dosage of ganglionic-blocking agents (2). The gradualness of the reduction in blood pressure and the absence of significant side-effects make reserpine in sustained-release form a decided asset in the treatment of mild and moderate hypertension.

SUMMARY

Fifty-five hypertensive patients were treated with reserpine in sustained-release form. In 28 patients below 60 years of age, the average blood pressure fell 33 mm. Hg (systolic) and 23 mm. (diastolic). In 27 patients 60 years of age or older, the average blood pressure fell 37 mm. Hg (systolic) and 16 mm. (diastolic). In both groups, accompanying symptoms (dyspnea, angina, edema, headaches) were greatly improved. Forty-one patients (74.6 per cent) had a good response to therapy, 7 (12.7 per cent) had a fair response, and 7 (12.7 per cent) had a poor response. Drowsiness was reported by 6 patients, nightmares by 1 and occasional nasal congestion by another. Two of the complaints of drowsiness and the complaint of nightmares disappeared upon reduction of the dosage. The other side-effects were not severe enough to warrant discontinuing the medication.

It is concluded that reserpine in sustained-release form is preferable to reserpine in conventional form in the treatment of mild and moderate hypertension, and that it is equally effective in geriatric and non-geriatric patients.

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THE USE OF AZACYCLONOL (FRENQUEL) IN THE TREATMENT OF MENTAL DISTURBANCES OF THE AGED: A DOUBLE-BLIND, CONTROLLED STUDY

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Early in 1955, Fabing (1) called attention to the peculiar properties of azocyclonol (Frenquel[1]). This compound appears to influence the thought processes rather than the mood of patients suffering from experimental and spontaneous mental illness. At the end of one year, Fabing and Hawkins (2) summarized the results of clinical trials with Frenquel in 115 private psychiatric patients. It was apparent at that time that Frenquel had a beneficial effect, especially upon hallucinatory and delusional phenomena, in some but not all patients suffering from schizophrenia, postoperative delirium, toxic psychoses and senile confusion states. This observation, particularly in the case of schizophrenia, was confirmed in double-blind, well-controlled studies by Rinaldi, Rudy and Himwich (3), Mason-Browne (4) and Odland (5). In our preliminary studies (6) we confirmed the findings previously published. Among the first 75 patients in our series treated with Frenquel, improvement occurred most often in the small number of confused, aged psychotic patients. The dosage employed was 60 to 240 mg. by mouth daily, usually following an initial period of intravenous administration in a dosage of 45 to 200 mg. daily.

Since elderly, psychotic patients had not been selected specifically for a double-blind test in previous investigations, we decided to conduct such a study.

CLINICAL MATERIAL AND METHODS

Of a total of 131 patients, 16 were observed without placebo or Frenquel therapy in order to make certain that the type of evaluation would be satisfactory. The other 115 patients were treated simultaneously with a medication labeled either "Frenquel X" or "Frenquel Z." The patients knew nothing of the differences in medications. The physicians concerned with grading the behavior of each patient knew only that there were 2 groups of patients, each receiving a different drug, but they did not know which, if either, of the compounds was a placebo. Both Frenquel and placebo were administered in a dosage of two 50-mg. tablets once daily upon arising. The average duration of treatment was 103.3 days, as shown in Table 1.

Of the 115 patients receiving medication, 61 were females and 54 were males. They were suffering from a variety of chronic mental illnesses and had been in a state hospital for a prolonged period. Their ages ranged from 52 to 96 years, with an average of 74 years. Seventy patients (38 females and 32 males) received Frenquel, and 45 (23 females and 22 males) received a placebo. The psychiatric evaluation of each patient included the state

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[1] Frenquel is the trademark of The Wm. S. Merrell Company, Cincinnati 15, Ohio for its brand of azacyclonol.

of orientation, memory, psychomotor activity, anxiety, tension, mood, amount of hostility, presence or absence of delusions, presence or absence of hallucinations, and nature of social behavior. At the end of each observation period, the patients were examined again to determine their relative progress. In this category, each patient was assessed according to whether or not his over-all behavior had become worse, had remained virtually unchanged, had undergone slight to moderate improvement, or had manifested great improvement. During the course of therapy, 2 patients improved sufficiently to be paroled from the hospital; 1 was in the Frenquel group and 1 was in the placebo group.

In Tables 2 through 10 the responses of males and females in the Frenquel and placebo groups are listed according to the foregoing categories. The 16 untreated patients were not included in the comparison, since there was no significant change in this group during or following the period of observation.

RESULTS

The general results of treatment, as outlined in Table 10, are discussed briefly for the purpose of clarity. Of the 32 male patients in the Frenquel group, 8 im-

TABLE 1. *Average Duration of Treatment*

Treatment	No. of Days of Treatment (average)
Frenquel—70 Patients	*107.2*
Females, 38	112.4
Males, 32	101.1
Placebo—45 Patients	*97.3*
Females, 23	95.4
Males, 22	99.2
Total No. of Patients (both groups)—115	*103.3*

TABLE 2. *Orientation*

	Frenquel group						*Placebo group*					
	Females (38)		Males (32)		Total (70)		Females (23)		Males (22)		Total (45)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
No impairment	3	7	14	15	17	22	0	0	11	11	11	11
Slight impairment	5	4	2	1	7	5	0	0	0	0	0	0
Gross impairment	30	27	16	16	46	43	23	23	11	11	34	34

TABLE 3. *Memory*

	Frenquel group						*Placebo group*					
	Females (38)		Males (32)		Total (70)		Females (23)		Males (22)		Total (45)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
No impairment	0	0	1	1	1	1	0	0	1	1	1	1
Slight impairment	11	20	21	21	32	41	2	3	14	14	16	17
Marked impairment	27	18	10	10	37	28	21	20	7	7	28	27

TABLE 4. *Psychomotor activity*

	Frenquel group						*Placebo group*					
	Females (38)		Males (32)		Total (70)		Females (23)		Males (22)		Total (45)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Increased	24	1	9	2	33	3	17	10	12	7	29	17
Normal	2	19	10	18	12	37	1	2	4	5	5	7
Decreased	12	18	13	12	25	30	5	10	6	10	11	20

TABLE 5. *Anxiety and tension*

	Frenquel group						*Placebo group*					
	Females (38)		Males (32)		Total (70)		Females (23)		Males (22)		Total (45)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Increased	7	0	1	1	8	1	2	21	2	20	4	41
None	31	38	31	31	62	69	1	22	2	20	3	42

TABLE 6. *Mood*

	Frenquel group						*Placebo group*					
	Females (38)		Males (32)		Total (70)		Females (23)		Males (22)		Total (45)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Elated	3	0	1	1	4	1	1	1	1	0	2	1
Appropriate	0	5	1	5	1	10	0	0	0	2	0	2
Labile	27	29	23	22	50	51	19	18	16	12	35	30
Depressed	3	1	2	0	5	1	0	0	1	1	1	1
Apathetic	5	3	5	4	10	7	3	4	4	7	7	11

proved markedly, 6 improved slightly to moderately, 17 remained unchanged, and 1 became worse. The results were even better in the female patients: of the 38 in the Frenquel group, 20 improved markedly (1 was paroled from the hospital), 10 improved to a slight or moderate degree, and only 8 remained unchanged.

Among the 23 females receiving the placebo, 1 showed marked improvement; 3, slight to moderate improvement; and 19, no significant change. Similar results were obtained in the 22 males given placebos: 1 improved sufficiently to be paroled from the institution, 2 showed slight to moderate improvement, and 19 remained unchanged. Of the 45 patients given placebos, 2 improved greatly, 5 exhibited slight or moderate improvement, 38 showed no change, and none was made worse.

In summary—among the 70 male and female patients treated with Frenquel,

TABLE 7. *Hostility*

	Frenquel group						*Placebo group*					
	Females (38)		Males (32)		Total (70)		Females (23)		Males (22)		Total (45)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
None	5	35	15	24	20	59	4	3	3	6	7	9
Slight	6	1	8	6	14	7	3	4	9	8	12	12
Marked	27	2	9	2	36	4	16	16	10	8	26	24

TABLE 8. *Delusions and Hallucinations*

	Frenquel group						*Placebo group*					
	Females (38)		Males (32)		Total (70)		Females (23)		Males (22)		Total (45)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Absent	4	30	11	21	15	51	0	1	2	4	2	5
Present	34	8	21	11	55	19	23	22	20	18	43	40

TABLE 9. *Social Behavior*

	Frenquel Group						*Placebo Group*					
	Females (38)		Males (32)		Total (70)		Females (23)		Males (22)		Total (45)	
	Before	After	Before	After	Before	After	Before	After	Be fore	After	Before	After
Normal	0	1	0	0	0	1	0	0	0	1	0	1
Slight	6	29	12	21	18	48	1	2	7	6	8	8
Marked	1	0	0	0	1	0	1	1	1	0	2	1
Seclusive	31	8	20	11	51	19	21	20	14	15	35	35

TABLE 10. *General Results*

	Frenquel group			*Placebo group*		
	Females (38)	Males (32)	Total (70)	Females (23)	Males (22)	Total (45)
Marked improvement	20	8	28	1	1	2
Slight improvement	10	6	16	3	2	5
No change	8	17	25	19	19	38
Worse	0	1	1	0	0	0

striking improvement occurred in 28, and slight or moderate improvement in 16; there was no change in 25, and 1 became worse.

As seen in Table 8, there was a decidedly beneficial effect from Frenquel therapy in the patients suffering from delusions and hallucinations. These manifestations were present in 34 of the 38 female patients, but following medication

persisted in only 8 (a 77 per cent reduction). Twenty-one of the 32 males receiving Frenquel were suffering from delusions and hallucinations at the beginning of the study, but by the end of the course of treatment the number had dropped to 11 (a 48 per cent reduction). In the placebo group, there was no significant diminution of hallucinations and delusions in the 23 females and a reduction of only 10 per cent (from 20 to 18 patients) in the males experiencing delusions and hallucinations. Thus, of the 70 male and female patients treated with Frenquel, 55 experienced delusions and hallucinations initially. At the end of the study, the total number of patients with delusions and hallucinations had dropped to 19—a reduction of 66 per cent. Less striking improvement resulting from Frenquel therapy manifested itself in improved orientation (Table 2), more appropriate mood (Table 6), decreased hostility (Table 7), and less seclusive social behavior (Table 9). Tension and anxiety occurred in only 8 patients but appeared to respond to Frenquel therapy in 7 (Table 5).

As shown in Table 1, although the average duration of treatment for all groups was 103.3 days, the length of the period varied slightly between the different groups. The slightly longer duration of the Frenquel treatment periods as compared with the placebo periods is a reflection of the greater ease of continuing drug therapy when a favorable response is being obtained.

DISCUSSION

Had the dosage of Frenquel been adjusted for optimum effectiveness in each case (which is not possible in a double-blind study), there probably would have been an even better response to therapy. Moreover, had the test course been over a longer period of time, greater improvement might have been manifest. The reason for the better results with Frenquel in the female group as compared to the male group (although the results in the males were better than in the comparable placebo group) is obscure at the present time. The complex, poorly understood alterations in endocrine balance of both males and females as they approach senility may well be of prime importance in explaining this difference. It is conceivable, however, that the slightly longer course of treatment or the more advanced age in the females (76.4 years as opposed to 71.8 years in the males), or both, influenced the results.

Toxicity. Complete blood counts, urinalyses, cephalin-flocculation tests and bromsulphalein tests were performed on 62 Frenquel patients and 29 placebo patients. One such group of tests was carried out prior to administration of the drug, and another, upon completion of the studies. In 6 of the patients, bromsulphalein values which were somewhat high initially had fallen appreciably by the end of the study; but in 7 other patients there was a significant rise in bromsulphalein values during the period of medication. In 3 cases the cephalin-flocculation test showed a four-plus reading in the forty-eight hours prior to the study and remained unchanged throughout. However, none of the changes was interpreted as indicating either a beneficial or a harmful effect upon the function of the various organ systems insofar as they could be tested by the usual laboratory methods.

Frenquel given orally appears to be a safe drug. Since it is also supplied as a

solution for intravenous use, additional data relative to its safety by this route were obtained during the course of many clinical tests. These data are not included in this report, but form the basis for the statement that we have observed no untoward effects from intravenous administration. In 1 case, some of the Frenquel liquid entered the surrounding tissues but caused no reaction. Because of the small fragile veins in many elderly people, we also tried administering Frenquel intramuscularly in doses of 1 to 3 cc.; again, we observed no ill effects.

SUMMARY AND CONCLUSION

A controlled, double-blind study involving 131 patients has shown that in the treatment of psychoses associated with the aging process, azocyclonol (Frenquel) is considerably more effective in elderly women than in elderly men in improving the general psychiatric status and, specifically, in reducing the number of patients with delusions and hallucinations. However, the drug is demonstrably more effective in aging men than is placebo medication in either men or women.

All patients in this series received 100 mg. of Frenquel orally, once daily upon arising, and the results were compared to those following placebo administration. The average duration of the test period was 103 days. Future studies should determine the optimum dosage of the drug and the proper duration of therapy.

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RAPID COLD PLASMA INFUSION TREATMENT FOR SEVERE SHOCK (PERIPHERAL FAILURE) FOLLOWING CORONARY OCCLUSION*

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One of the most appalling emergencies with which the physician is confronted is the patient with coronary occlusion in a state of severe shock. In this category one finds the lowest percentage of recoveries. Most authorities agree that the mortality rate is at least 80 per cent (1–3). The patient presents a clinical picture of collapse—cold, clammy and markedly cyanotic skin; unconsciousness or, at best, a semi-comatose state; a weak pulse with distant heart sounds; and a systolic blood pressure of 80 mm. Hg or less. Veins are collapsed and venous pressure is markedly reduced (1). When the cyanotic skin or the mucous membranes are pinched, a dead-white blanching ensues, and this white area remains unchanged for a considerable period. The state of shock can also be accompanied by a severe precordial crushing sensation, although in some instances there is little or no distress of this sort. The patient can lie in a horizontal position with little or no dyspnoea, and veins in the neck are not distended.

A patient may progress from a state of peripheral failure to one of congestive failure as the hours go by. In this article it is the intention of the author to deal solely with the initial phase of cardiac shock preceding congestive failure.

Conventional treatment (2) has usually consisted of the following features:

(a) Rest: The patient is placed in as comfortable a position as possible, and not moved more than necessary.

(b) Warmth: Warm blankets are placed around the patient to help combat the symptoms of shock.

(c) Morphine (or a combination of morphine and atropine) is administered either subcutaneously or intravenously, to relieve anxiety and combat shock.

With these methods, the shock will often be relieved in a period ranging from a few hours to a day or more, but the great majority of patients do not survive the attack.

More recently, various vasopressor drugs such as Neosynephrine, norepinephrine, mephentermine sulphate and *d*-desoxyephedrine have been used intravenously in an attempt to allay the peripheral vascular collapse by causing vasoconstriction. The author must confess that he has been disappointed with the results obtained with these drugs. They allay the cyanosis and cause pallor of the skin due to vasoconstriction; they also raise the blood pressure to some extent. However, there appears to be relatively little positive inotropic effect upon the

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heart, and much valuable time may be lost in this way. Those who use sympathomimetic agents in an attempt to break down this shock cycle or prevent its becoming "irreversible" do not claim survival in more than half of their cases (2).

Schwartz (4) in 1947 described a case in which 2,200 cc. of plasma and whole blood was administered intravenously within forty minutes, and in which the state of peripheral failure was transformed to one in which the cyanosis and hypotension were completely relieved. A subsequent electrocardiogram revealed acute coronary occlusion.

In this paper he displays excellent logic in justifying the procedure. After all, this state of peripheral failure is characterized by:

(a) Pooling of a large percentage of the total blood in the peripheral vessels.

(b) Lowered venous pressure.

(c) Poor venous return to the heart.

(d) A relatively small percentage of the total blood in actual circulation.

(e) Greatly lowered minute output of the heart.

(f) Undoubtedly poor coronary perfusion—by virtue of lowered aortic diastolic pressure and possibly by increased blood viscosity.

(g) A pulmonary circulation time which is normal or even faster than normal—from which it may be concluded that there is no loss of pulmonary arteriolar tone (1).

All the foregoing factors have been checked by various clinical investigators, and it would be redundant to go further into their methods of treatment and results at this time.

CLINICAL DATA

Being impressed by the result obtained by Schwartz in this case, and being even more impressed with his reasoning, the author adopted his method of rapid plasma infusion—at the rate of 60 to 80 cc. of plasma per minute, or as fast as the drip apparatus will function with the stopcock removed. The results were far better than those obtained with any previous management. Usually in about an hour, the shock had abated considerably. The only disadvantage lay in the fact that very large quantities of plasma or other intravenous solutions were used. When a man aged 60 with a history of coronary thrombosis some years before (Fig. 1), was seen in a state of deep shock with a systolic pressure of 40 mm. Hg, the case appeared so urgent that he was immediately given plasma at the rapid rate recommended by Schwartz, but the plasma was in its cold state, fresh from the blood bank. It was felt that there was no time to warm the solution. The result would need to be seen to be believed. Within thirty seconds, the deep cyanotic colour of the skin and mucous membranes was replaced by a natural pink, the patient became fully conscious, and his blood pressure at the end of one minute was 100/70 mm. Hg. His heart sounds were much stronger and quite regular. The improvement was so marked and so rapid that only 250 cc. of plasma was infused; no more was needed, as his recovery was uneventful. This procedure, born of desperation, was used in 2 more cases.

One man aged 70, whose normal blood pressure was 166/78 and who had been under treatment for coronary insufficiency (Fig. 1), was seen in a state of com-

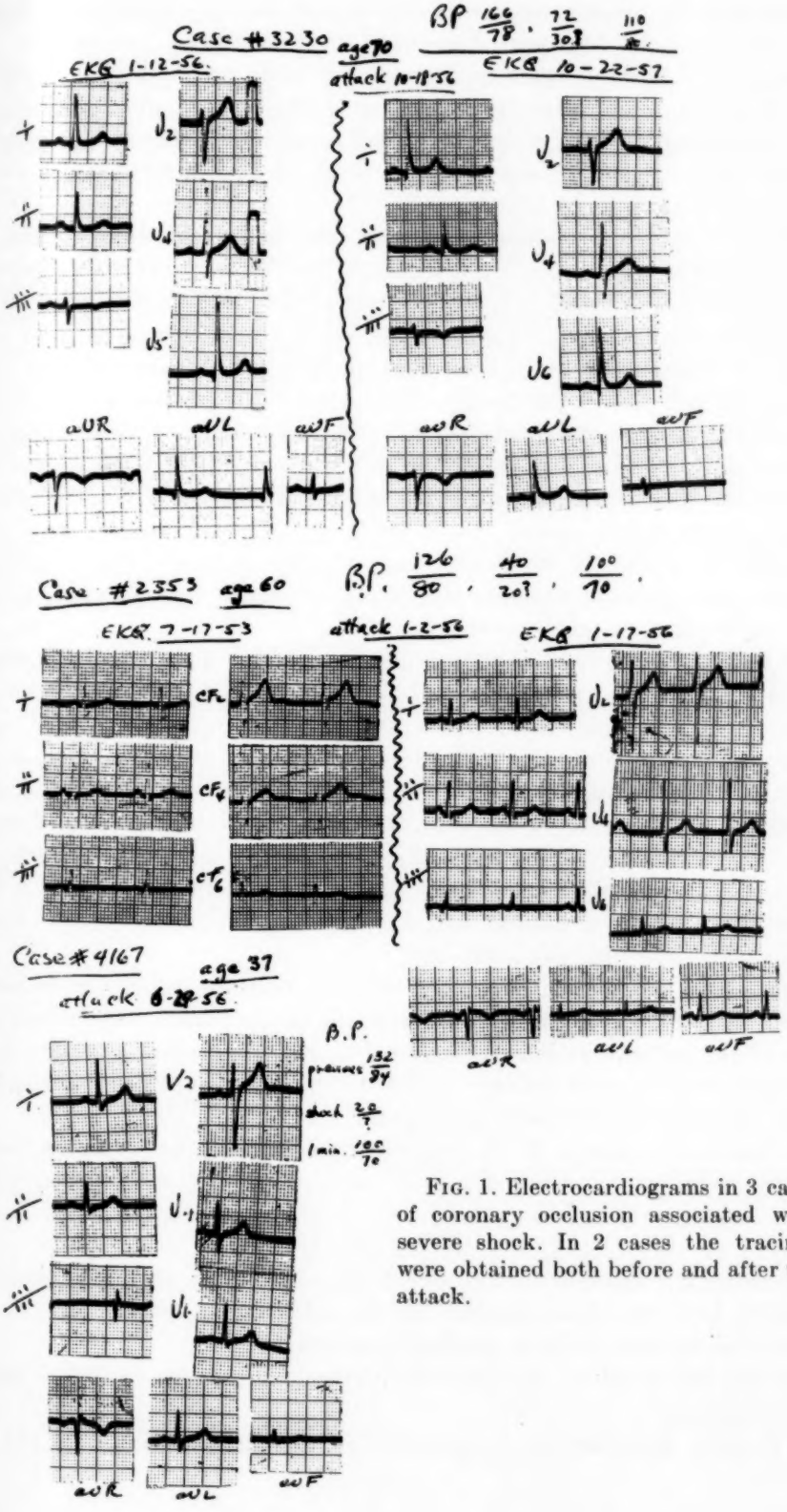

FIG. 1. Electrocardiograms in 3 cases of coronary occlusion associated with severe shock. In 2 cases the tracings were obtained both before and after the attack.

plete collapse. His blood pressure was 72/30; but upon administration of 250 cc. of cold plasma at the rapid rate it rose to 110/80 in about a minute.

Another man aged 37 was seen immediately after he had such an attack, at which time his systolic pressure was 20 mm. Hg, and his heart sounds could hardly be detected (Fig. 1). He was rushed in an ambulance to the emergency ward and 250 cc. of cold plasma was given by the described method. His recovery was as rapid as that of the others.

All 3 patients, after becoming conscious, shivered violently and then broke down into a fit of sobbing for a few minutes. There were no other side-effects.

Since recovery occurred so rapidly (between thirty and sixty seconds after the rapid cold plasma infusion was begun), and since it was effected with the first 40 to 80 cc. of infusion fluid, it is somewhat unlikely that venous collapse and the other factors mentioned previously could have been corrected so quickly. It seems more likely that the rapid cold infusion (supplying a temperature gradient of around 54°F.) either stimulated the heart muscle directly, or acted reflexly (possibly through the afferent vagal fibres located near the S-A node where the fluid entered the right auricle). It is possible that once the heart was stimulated (either directly or reflexly) to make a series of stronger contractions, the cerebral anoxia was relieved with benefit to the vasomotor centre, and the normal state of circulatory haemodynamics was restored.

In view of the hypothesis that the sooner the stage of deep shock is relieved, the less will be the permanent infarction damage, it should not be surprising that in these 3 patients who recovered so rapidly from shock, subsequent electrocardiograms did not show any infarction damage. One of the patients had suffered at least 1 previous infarction and another had been treated for coronary insufficiency. In Figure 1, the electrocardiograms before and after these episodes are shown for 2 of the cases; for the third, only the tracing taken afterwards is shown, since there was no suspicion of any previous cardiac lesion. It is highly probable that the third patient had a subendocardial infarction, as later an embolus developed in his left lower leg.

In the 3 cases cited here, the author was fortunate in being able to institute treatment within ten, twenty-five, and thirty-five minutes, respectively, after collapse of the patient. It is conceivable that, had this treatment been delayed for a longer period of time, definite myocardial damage from the infarction would have been revealed in the electrocardiogram.

This treatment appears to be less expensive than other infusion methods which require larger quantities of plasma, with or without whole blood.

SUMMARY

Three successive cases of coronary occlusion with severe shock and peripheral failure have been treated successfully by the following method:

(a) Immediate removal to a hospital emergency ward.

(b) Rapid (60 to 80 cc. per minute) intravenous infusion of 250 cc. of cold (4°–6° C.) plasma.

It is thought that the low temperature of the plasma stimulates the heart

either directly or reflexly to produce stronger contractions, thus rapidly dissipating the state of peripheral failure.

It is suggested that the size of the myocardial area which becomes infarcted may vary with the length of time the patient is in a state of shock; and that, by relieving the shock as rapidly as possible, the infarct may be minimized.

Addendum

The small diameter of the plastic tubing in some intravenous sets may make it difficult or impossible to achieve the rate of flow specified in this article. In this connection, I would recommend the Baxter R-48 drip apparatus. The drip chamber contains a good volume of liquid and is made of readily compressible plastic instead of glass. If this chamber is squeezed rapidly three or four times, the volume of flow attained should be satisfactory. The pressure behind the infusion has no ill effect.

Subsequent correspondence in response to the original article leads me to believe that very cold (less than 5° C.) 6 per cent Dextran or dilute human albumin (when obtainable) should be as efficacious as plasma—and certainly much less expensive.

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SUPPORTIVE ADRENOCORTICAL STEROID THERAPY IN ACUTE AND SUBACUTE CEREBROVASCULAR ACCIDENTS, WITH PARTICULAR REFERENCE TO BRAIN-STEM INVOLVEMENT

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Over the past decade, clinicians, neurologists and neurosurgeons have been seeking all possible logical or empirical methods for improving the plight of the patient suffering from a massive stroke. As a result of this emphasis, an inroad has been made into the previous fatalistic attitude. Much has changed since Penfield commented, "The right of the aged and the hypertensive to die from apoplectic stroke undisturbed has been unchallenged for a very long time."

I am keenly aware of the many misgivings and reservations pertaining to any therapy that is advocated for the acute and subacute phases of cerebrovascular ischemia or infarction, with or without an associated thrombosis or embolism. During the past few years, we have witnessed the ebb and flow of interest in stellate ganglion blocks; papaverine; nicotinic acid; intravenous histamine, procaine, aminophylline, or bicarbonate; inhalation of external or autogenous carbon dioxide; and anticoagulants. Each of these forms of therapy has been associated with a variable measure of success, as described in enthusiastic reports by capable observers. On occasion, the response of individual patients has been quite dramatic. The enthusiasm aroused for such therapy was dampened in short order, however, by a volley of criticisms voiced by other authorities. The greatest objections concerned the unpredictable course of acute nonhemorrhagic stroke in any given patient, and the failure of the treatment being advocated to lower the rates of morbidity and mortality significantly as compared with the rates in control groups of patients.

Inasmuch as the author also found himself in the position of voicing similar arguments to his own colleagues, he waited two years after observing the striking effects of adrenal steroids in the first patient of his series before feeling justified in reporting these experiences in the form of a paper which includes the data on additional cases of favorable response observed in the interim. To date, the article by Russek *et al.* (1) appears to be the only one in the standard literature dealing exclusively with the use of cortisone in the immediate treatment of apoplectic stroke. Very few studies have come to my attention in which the adrenocortical steroids were actively employed in the subacute hemiplegic phase of stroke (2, 3). Several reviews were published in 1956 and 1957 dealing with the management of cerebrovascular accidents; in 1 instance (4) no reference was made to the use of hormones, and in the other 2 only a sentence was devoted to the entire subject (5, 6). Indeed, the value of such therapy in cerebral infarction has actually been denied in some quarters (7).

It should be emphasized that the use of cortisone and its analogs is not advo-

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cated as the sole therapy, or as a unilateral approach by practicing physicians, for the management of stroke in these severely-ill patients. These drugs are no more than a temporary measure in the treatment of certain patients with cerebral insufficiency and infarction by clinicians who are familiar with the methods of administration, and who are cognizant of the many potential complications. The most significant aspect of this report is the apparently unique value of hormonal therapy in those acute and subacute cerebrovascular accidents which predominantly involve the brain stem. There is still no such thing as a panacea for the amelioration of all cerebral infarctions; every therapeutic attempt will inevitably fail in many of these cases. For example, my experience has not been very encouraging in several cases of acute or subacute middle cerebral artery syndrome, and in hemiplegias of over six months' duration.

In the light of this orientation, it was considered best to present the following 9 case reports to illustrate the improvement that may be expected with hormonal therapy, and to avoid the errors involved in a statistical breakdown of the results in all the patients treated in this relatively small series. Moderate improvement was observed in an additional 6 patients (briefly referred to in the discussion). There was no significant change in 5 other moribund or severely-ill patients. It is hoped that this report will encourage others to present their own experiences with this mode of treatment.

CASE REPORTS

Case 1

L. B., a 79-year-old retired engineer, was seen in consultation during his second hospitalization at the Good Samaritan Hospital because of a progressively rapid downhill course. He had been seen approximately four months previously at the time of his first hospitalization by another internist and by a neurosurgeon who concurred that the patient had hypertensive encephalopathy with multiple small hemorrhagic infarcts in the basal nuclei, producing a pseudobulbar type of palsy. At that time, all the attending and consultant physicians expressed grave doubts about the patient's immediate prognosis.

When I first saw the patient in February 1956, he exhibited evidence of hypertensive vascular disease with an enlarged heart; repeated cerebral thrombosis with profound pseudobulbar palsy; collapse and probable pneumonitis of the left lower lobe of the lung, associated with marked leukocytosis; and azotemia related to the fever, dehydration, nephrosclerosis and probable pyelonephritis. He could hardly swallow; therefore gastric intubation was recommended. His speech was utter jargon. Drooling was marked, and he could not expectorate any of his pharyngeal secretions. He was expected to survive for only a short period of time.

In view of the patient's critical status, with particular reference to the presence of his profound bulbar symptoms, he was given not only massive penicillin and streptomycin therapy, but also cortisone acetate intramuscularly, 50 mg. every eight hours. Within sixteen hours there was a profoundly gratifying improvement in his speech and swallowing mechanisms. His fever had also abated considerably. He was not only able to swallow without difficulty, but for the first time in over six months, he could expectorate the secretions from his pharynx and tracheo-bronchial tree. In view of the obvious infection and also a latent diabetes mellitus, the dosage of cortisone acetate was reduced to 25 mg. intramuscularly every eight hours; this was continued for another two days. At that time, prednisolone (Sterane) was started orally in a dosage of 5 mg. every six hours. Because of his progressively favorable course, the prednisolone was reduced to 5 mg. every eight hours.

Multi-vitamin therapy and oral sulfonamides were also prescribed. There were no overt complications from the therapy.

The patient was discharged to his home three weeks following the institution of cortisone therapy. At home, he subsequently exhibited evidence of mild congestive failure, for which he was digitalized and given frequent mercurial injections. Sterane therapy was maintained, however, because shortly after discontinuance, the bulbar symptoms had recurred. Sterane was continued for over nine months and the patient fared as well as could possibly be expected. There was a subsequent short admission for mild heart failure—more for the convenience than the actual necessity. He was last seen in October 1957, because of acute sciatica. Aside from a mild depression and his advanced age, it was difficult to realize that he was the gravely-ill patient we had attended eighteen months earlier.

Case 2

A. A., a 58-year-old married white female, was first seen in consultation with her surgeon on November 14, 1956. She was in a comatose condition of several hours' duration, and pulmonary edema was present. She was known to have mild hypertension, but she had taken no medication for some time. Twelve hours prior to my seeing her, she had slipped on a slick floor and fallen on her outstretched hand, sustaining a simple fracture of the left radius. This fracture was reduced without apparent complication, after which she was given a small dose of analgesic parenterally. She then went home and fell asleep; but subsequently she could not be roused, and her comatose condition and stertorous breathing were discovered.

Physical examination revealed a well developed and somewhat overweight middle-aged white woman with marked stertorous breathing. She did not respond even to maximum stimulation. The pulse was 92 and regular. The blood pressure had fallen precipitously from approximately 130 mm. (systolic) when the surgeon first recorded it, to 50 mm. by the time of my arrival. Both pupils were pin-point sized. There was moderate xanthelasma of one eyelid. The arterioles of the optic fundi and the fundi themselves were not remarkable. No evidence of head trauma could be found. The tongue had not been bitten. Only minimal resistance to complete anterior flexion of the neck was encountered. There were extensive coarse rhonchi and rales throughout both lung fields. The heart sounds and peripheral pulsations were not remarkable. The cast which had been applied over her left hand, wrist and forearm at the site of the fracture of the radius was in satisfactory condition. All normal reflexes were absent. There was no localized palsy of either the face or the extremities. The Babinski response was present bilaterally.

Prior to being sent to St. Mary's Hospital she was given 100 mg. of cortisone acetate intramuscularly, 100 mg. of nicotinic acid intramuscularly, and 15 mg. of N-allyl-normorphine (Nalline) intravenously. Her blood pressure on arrival at the hospital was less than 50 mm. Hg systolic; intravenous levarterenol (Levophed) was accordingly started. A good pressor response was achieved, but her condition was still considered to be critical. She was given another injection of cortisone (100 mg.), following which the dosage was 75 mg. every six hours. She concomitantly received nicotinic acid, 50 mg. intramuscularly every two hours, and prophylactic antibiotic therapy. Frequent aspiration of the oropharynx was required.

Over the course of the next twelve hours, the patient became increasingly responsive to her environment and began to exhibit good motion in all her extremities. Reflexes were hyperactive throughout, and the Babinski response persisted bilaterally. There was no nuchal rigidity. The leukocyte count was 33,750, with 91 per cent polymorphonuclear cells. Intravenous levarterenol was required for approximately thirty-six hours, however, in view of the markedly labile blood pressure. As the clinical picture improved, the cortisone was injected only every eight hours, and then administration was changed to oral cortisone in a dosage of 25 mg. every eight hours for three more days. Oral niacin-pentylenetetrazol (Nicozol) and parenteral vitamin B_{12} were also administered. The serum cholesterol level was 298 mg. per 100 ml. No overt complications were noted during the remainder of her

hospital stay and the neurologic findings reverted to normal. She was discharged approximately one week following admission.

Case 3

W. H., a 57-year-old retired government worker, was seen at home for the first time in a state of complete coma of several hours' duration, associated with Cheyne-Stokes breathing, incontinence and marked stertorous breathing. The initial history was non-contributory as given by his wife, who stated that the patient had been in good health to the best of her knowledge up to the time of the present episode. There had been no known convulsive seizures. The patient was immediately hospitalized, although it appeared questionable that he would arrive at St. Mary's Hospital alive.

Physical examination revealed a well developed and well nourished ruddy middle-aged white male, who did not respond even to maximum stimulation. His pupils were pin-point, although the fundal arterioles and discs were not remarkable. The neck was supple. Coarse rhonchi were heard throughout both lung fields. The Cheyne-Stokes breathing persisted. All the extremities were flaccid, and the body reflexes were depressed. No pathologic reflexes or localized pareses were noted on admission. The blood pressure was 110/80. The pulse was 112 and regular.

It was my initial impression that the patient had had a massive cerebral infarction, although the possibility of a cerebral embolus was subsequently entertained because of the history of recent substernal distress. The patient was placed in an oxygen tent, and the oropharynx was constantly aspirated. His temperature rose to 102° F. rectally. This was associated with a white blood cell count of 17,300, of which 91 per cent were polymorphonuclear cells. Cortisone acetate was started in a dosage of 100 mg. intramuscularly every eight hours, along with prophylactic antibiotics. Within eight hours, the patient was responding to questioning. His condition was still considered critical, particularly in view of the rising temperature. By the next day, however, the clinical improvement was remarkable in all respects—most notably in the mental and neurologic spheres. He was carefully questioned about recent vague distress in the anterior chest wall, but no definite coronary episodes could be established. There was evidence of a possible old healed posterior-wall myocardial infarction, but the tracings remained stable in several subsequent electrocardiograms. By the third day, the dosage of cortisone was decreased to 50 mg. every eight hours intramuscularly, and it was discontinued two days later. The patient refused a lumbar puncture. As his clinical course continued to improve, he was allowed out of bed. He was discharged home undergoing treatment with other conservative non-hormonal measures following his eighth hospital day.

Case 4

R. K., a 76-year-old white widow, was admitted to the Good Samaritan Hospital in a state of complete coma and early pulmonary edema. Her son stated that she had been getting along fairly well until several hours prior to admission, when her progressively comatose condition was first appreciated. There had been no actual seizures or incontinence. She had been known to have hypertension for a number of years, but had not recently taken any medication except an occasional vitamin preparation. There was no history of pain in the chest.

The patient was an elderly obese white female in a comatose condition, reflexly responding only to maximum stimulation. Her breathing was stertorous, and there was considerable frothing at the mouth. The pupils were miotic, but reacted to light. Marked arcus senilis was present. The fundal arterioles were moderately sclerotic. Coarse rhonchi with occasional asthmatic breath sounds were heard bilaterally. The heart was not enlarged or otherwise remarkable. The patient was completely flaccid and the tendon reflexes were absent. There was a definite Babinski response on the left and a questionable Babinski response on the right. The pulse was 72 and regular. The blood pressure was 112/72.

The patient was obviously critically ill, and it appeared unlikely that she would survive the evening. She was placed in an oxygen tent, and given prophylactic antibiotics. Cortisone acetate was started in a dosage of 50 mg. intramuscularly on admission, and every eight hours thereafter. The response over the ensuing ten hours was remarkable. Mental capacity and the ability to eat without discomfort returned by the second hospital day. Cortisone was discontinued following the third hospital day, at which time oral nicotinic acid and parenteral vitamin B_{12} therapy was started. The blood pressure was never within the hypertensive range. The patient was discharged home on her sixth hospital day.

Case 5

I. S., a 45-year-old white female, was admitted to the Good Samaritan Hospital on September 7, 1957, with a history of progressive left shoulder pain and weakness, increasing weakness of the left lower extremity, severe occipital headache, opisthotonos due to tonic contractions of the neck and upper spinal muscles, and increasing vascular collapse—all within a period of a few hours. The patient had been studied several weeks previously because of the possibility of angina pectoris, but 3 electrocardiograms and 3 serum transaminase determinations were all within normal limits.

The most urgent problem shortly after admission was treatment of the shock by continuous intravenous levarterenol (Levophed), and management of the recurrent severe opisthotonos by intravenous infusions of amobarbital sodium (Amytal). During the course of these procedures, the patient was found to have nystagmus (with the slow component toward the left side), flattened nerve heads in the fundoscopic examination, flaccidity of the left arm and left leg, no response to pain or pinprick throughout the left side of the body, no abdominal reflexes, and bilateral Babinski responses. An electrocardiogram shortly after admission revealed evidence of extensive subendocardial ischemia. Although initially it was felt (on the basis of the recent chest pain) that the patient was suffering from cerebral embolism, further consideration (particularly with the neurologic consultant) led to the belief that there was an embolus in the basilar artery system. This diagnosis was based on the presence of the severe occipital headaches and the opisthotonos caused by extreme spasm of the nuchal muscles.

The outlook appeared to be grim in view of the profound shock, the increasing coma, and the progressive neurologic manifestations involving the brain stem. Survival for more than a few hours was seriously questioned by all 3 physicians who saw the patient. Accordingly, cortisone acetate was started in a dosage of 100 mg. intramuscularly every six hours, along with intramuscular nicotinic acid. Intravenous amobarbital sodium (Amytal) was given also, as convulsions and opisthotonos had increased. Within eighteen hours after the institution of this therapy, there was recovery of consciousness, some improvement in the motion of the left upper extremity, and even a reduction in nystagmus. Levarterenol (Levophed) was still required to maintain the systolic blood pressure above 90 mm. Hg, however. By the following day, the paralysis improved, and she was able to swallow and speak.

A second electrocardiogram taken on the following day indicated further subendocardial ischemia. Because of this, and the improbability of intracranial bleeding, intravenous heparin was given in the hope that it might favorably influence both the myocardial and the cerebral lesions. An electrocardiogram on September 12, 1957 revealed almost complete restitution to the normal pattern. Beginning on September 14, the dosage of cortisone was progressively decreased to 25 mg. every twelve hours. (Heparin was stopped on September 13.) Oral prednisolone (Sterane) was then given, with a progressive reduction in dosage from 20 mg. daily to 5 mg. daily over a twelve-day period. The total duration of steroid therapy was three weeks.

The patient's subsequent course was one of gradual rehabilitation, particularly with reference to the severe occipital headaches and the muscular weakness in the previously paralyzed left limbs. She required several weeks of treatment by cervical traction and "spasmolytic" agents. A final electrocardiogram was interpreted as being within normal limits. She was discharged from the Good Samaritan Hospital on October 24, 1957.

Case 6

I. P., a 67 year-old single retired librarian, was initially seen approximately twelve hours prior to hospitalization, at which time she appeared to be recovering from a transient non-localizing cerebrovascular accident, manifested primarily by sudden weakness, nausea and difficulty in walking. The blood pressure at that time was approximately 240/110 mm. Hg and she had no difficulty in talking. Bed rest and oral niacin-pentylenetetrazol (Nicozol) were recommended. Approximately eleven hours later, I was again called to see her. At that time, there was evidence of hemiparesis involving the right upper and lower extremities. This was associated with some slurring of speech and a Babinski sign on the right side. She appeared to be clear mentally and had no headache or stiffness of the neck. The patient was known to have had hypertension for approximately seven years, but had taken no antihypertensive medication for some time. She was admitted to the Good Samaritan Hospital, in view of the apparent progressive nature of the cerebral injury.

The patient was a well developed and well nourished elderly white female with right-sided hemiparesis and considerable dysarthria. The blood pressure was 210/106 mm. Hg. The pulse was 76 and regular. The pupils were not remarkable. The fundal arterioles showed a considerable degree of angiosclerosis, but there were no actual hemorrhages, exudates or papilledema. The heart and lungs were not remarkable. Right-sided reflexes were hyperactive.

It was elected to observe the patient during a regimen of bed rest, mild sedation as needed, and oral Nicozol therapy for several days, pending further decisions. Over the first few days, the right hemiparesis persisted, and even appeared to be getting worse. The patient was very depressed, but otherwise there was no change. Prednisolone therapy (Sterane) was started in a dosage of 5 mg. every six hours orally, along with parenteral vitamin B_{12}. By the next day, speech had improved markedly, as had the paresis in the right leg. Because of moderate albuminuria on one occasion, the dosage of Sterane was reduced to 5 mg. every eight hours two days later. By the next day, however, there was a definite relapse in the paralysis which had again affected her right upper and lower extremities.

At this point, steroid therapy was changed to cortisone acetate, 50 mg. intramuscularly every eight hours. The patient was observed very closely, especially in regard to blood pressure and renal function. After receiving only 3 doses of cortisone, there was striking remission in the paralysis and the state of profound depression. Four days later, therapy was changed from cortisone to oral Sterane, 5 mg. every six hours, which she continued to take for approximately two weeks longer, both during and following her discharge from the hospital. The medication was then discontinued. A remarkable degree of improvement had taken place in the paralysis and in the mental outlook.

Case 7

D. S., a 56-year-old normotensive housewife, was first seen eight months following a left hemiplegia for which numerous vitamins, medicines and physiotherapeutic treatments had been recommended by several physicians, but to no avail. Not only was she bed-ridden, but she was mentally depressed and painful secondary contractures had developed. She responded but slightly to antianemic medication, niacin-pentylenetetrazol (Nicozol), forced fluids, antibiotics (for concomitant urinary tract infection) and passive exercises over a five-month period of personal observation.

When it appeared unlikely that any further help could be obtained from these procedures and that the patient was becoming increasingly despondent over her lack of progress, steroid therapy was begun. A single injection of cortisone acetate was followed by prednisolone (Sterane) in a dosage of 10 mg. thrice daily. Within a week, there was profound improvement in strength and motion of the left side. There was also complete abatement of the pain and tremor in the affected limbs that had previously been very troublesome. The dosage of the Sterane was reduced one week later to 5 mg. four times daily, and in another week it was decreased still further to 5 mg. three times daily. During this period,

the patient also received 80 units of corticotropin-gel every two weeks. Oral steroid therapy was administered for a two-month period, during which time the physiotherapist succeeded in getting the patient to walk with only slight assistance. In the same period there had been a dramatic alleviation of the mental depression. The urinary-tract infection appeared to be adequately checked by sulfonamide therapy.

Case 8[1]

H. W., a 75-year-old retired white male, was admitted to the St. Mary's Hospital on December 11, 1956 because of dizziness and vomiting of two days' duration. His condition had been initially diagnosed as hypertensive cardiovascular disease with left heart failure and chronic bronchial asthma. After several days of observation, during which he received small doses of reserpine (Serpasil), it was noted that the secretions in his throat were increasing, and that there was considerable slurring of speech. Frequent oropharyngeal aspiration was required, along with administration of antibiotics and oxygen. The following day it was discovered that the patient had right-sided facial paresis and was unable to swallow. That night, it was necessary to perform a tracheotomy in order to alleviate the respiratory distress. Anticoagulant therapy was then started but no significant improvement could be noted over the ensuing several days.

A consultation was obtained from the visiting neurologist, who made the diagnosis of thrombosis of the right posterior inferior cerebellar artery. This diagnosis was based upon the presence of right facial paresis, dysphagia and dysarthria, bilateral nystagmus, loss of pain sensation involving the left side of the face, and right hemiparesis. In view of the fact that the patient's condition was becoming worse, prednisone (Meticorten) was started in a dosage of 10 mg. every six hours. By the following day the patient's color had improved considerably and he was able to swallow and speak. His neurologic condition improved over the ensuing week, during which time the patient was able to swallow liquids without difficulty. The dosage of Meticorten was gradually reduced to 7.5 mg. every six hours, and then to 5 mg. every six hours. He was subsequently given corticotropin-gel intermittently for several weeks before discharge to a convalescent home. It was the opinion of the neurologist that such a dramatic improvement in ability to breathe, swallow and speak could hardly be considered coincidental, and that it was most likely due to the hormone therapy rather than to the other measures which had been previously instituted.

Case 9

W. K., a 56-year-old white male, was seen in consultation with his neurologist at a nursing home, specifically for the purpose of evaluating the possible benefit of steroid therapy. The patient had had repeated cerebral infarcts over the previous few years, resulting in extreme emotional lability. He had moderately severe pseudobulbar palsy that made his nursing care very difficult, particularly with reference to his inability to swallow either liquid food or his saliva without the fear of aspiration, his rigidity, and his incomprehensible jargon. There was a history of previous intermittent grand mal seizures over a long period of time; for this condition he was being treated with diphenylhydantoin (Dilantin). Babinski's sign was present bilaterally. The rest of the findings on physical examination were not remarkable. Blood pressure was normal, and the pulse was regular. The funduscopic examination revealed no abnormalities. No significant degree of prostatic enlargement could be found. A complete blood count and the results of urinalysis were within normal limits. The serum nonprotein nitrogen level was 56 mg. per 100 ml.

In view of the prolonged duration of the pseudobulbar palsy, the past history of seizures, and the possible mild dehydration, it was elected to observe the patient first during a treatment with niacin-pentylenetetrazol (Nicozol), daily parenteral vitamin B_{12}, hydra-

[1] I am grateful to Dr. Edgar Kellerman and Dr. Joseph Skyer for permission to cite this case.

tion, and other nonspecific measures for a "control" period of one week (even though many of these agents had been previously employed without benefit). When no improvement occurred during this period, a trial course of prednisolone (Sterane) was started in a dosage of 5 mg. thrice daily. Oral antacids, between-meal feedings, and supplementary potassium chloride were also given.

Within the next few days striking improvement occurred in the patient's appearance, speech, swallowing, rigidity, and affect. For the first time since he had been in the nursing home, he arose spontaneously and walked a few steps unaccompanied. No seizures were observed. A complication, however, was the development of marked (nondiabetic) polyuria, presumably on the basis of the increased ingestion of both solid food and liquids. This polyuria persisted in spite of attempts to reduce the dosage of the hormone. In fact, it proved to be so disconcerting to the limited nursing personnel that they and the family requested that the medication be stopped. The patient subsequently suffered a relapse to his previous status.

DISCUSSION

The author feels that his experience has covered a sufficiently large number of patients suffering from cerebrovascular accidents to warrant the following 3 statements:

1. The cases cited in this report had experienced nonhemorrhagic and nonembolic cerebral infarctions, with or without true vascular thrombosis. In over 60 per cent of cerebral infarcts studied at postmortem examination, no intra-arterial thrombus can be demonstrated (5, 8, 9). On the other hand, several eminent neuropathologists believe that an occluded vessel can almost always be demonstrated by careful study, provided death has been recent (10).

2. Death was to be expected within a few hours in those patients who exhibited pulmonary edema, profound coma of several hours' duration, Cheyne-Stokes respirations, areflexia, falling blood pressure, and evidence of severe brain-stem injury during the acute stroke phase. All clinicians of experience can attest to the great degree of error involved in dogmatic pessimistic prognosis. It has been shown, however, that whereas the depth of the coma may sometimes be unrelated to the patient's survival, the duration of coma is of considerable importance in this regard—particularly when it exceeds two hours (11). Prolonged periods of abnormal respiration, especially of the Cheyne-Stokes type, are also an ominous sign.

3. It is most unlikely that the remissions observed during steroid therapy were spontaneous. Most of these patients with acute or subacute strokes had first been observed over "control" periods ranging from days to months, during which most other modalities of conservative treatment had already been tried, to no apparent avail. I have rarely witnessed such dramatic improvement in stupor, depression, apathy, paresis, aphasia, impaired deglutition, and clouded consciousness within a 12- to 24-hour period during nonhormonal therapy in cases of severe brain-stem injury.

Mode of action of adrenocortical steroids

At the present time, explanations of the beneficial action of the adrenocortical steroids in acute cerebrovascular insufficiency and infarction are within the

realm of speculation. Russek and his colleagues (1) believe that the benefit is in large measure due to the prevention or prompt elimination of interstitial cerebral edema, the importance of which has been stressed by Hicks and Warren (8). This permits the early restitution of a considerable degree of neurologic function, both directly and by minimizing the damage to the nerve cells until collateral channels begin to serve the ischemic area. It would appear reasonable to assume that the favorable results observed in cases of brain-stem injury can be largely attributed to alleviation of edema in this vital and confined area.

Adrenocortical hormones, in addition to their effect in sustaining blood pressure, may also influence the tone and permeability of the smaller blood vessels. This is best exemplified by their beneficial effect in pseudohemophilia and in other hemorrhagic states (12). Animal experiments dealing with the action of cortisone on induced cerebral injury (13) and myocardial infarcts (14) have shown that cortisone has an inhibitory effect on cerebral mesenchymal edema and that it enhances the development of greater collateral circulation in the heart.

In the cases of subacute hemiplegia treated with adrenocortical steroids, the salutary effect was probably influenced by several additional factors, such as the improved motivation and increased sense of well-being that so frequently accompany the use of steroid therapy. Many of these patients had painful "frozen" shoulders, arthropathies, contractures, and shoulder-hand syndromes (reflex sympathetic dystrophy). These conditions are often ameliorated by administration of cortisone or its related compounds.

Methods of administration

In our series the most favorable results were obtained with intramuscular administration. Parenteral corticotropin-gel and oral prednisolone or prednisone were also used in several of these cases with varying success; the benefit appeared greater in ambulatory patients. In the severely-ill hospitalized patients who are seen for the first time, however, one can be most certain of achieving the desired effect with intramuscular cortisone.

Our policy has been to institute treatment with 75 to 100 mg. of cortisone acetate injected into the deltoid muscles every six to eight hours. When a beneficial effect is observed, the dosage is decreased as rapidly as feasible. In most of the patients, steroid therapy is changed to oral cortisone or prednisolone by the fourth day. (Triamcinolone was not available at the time of this report.)

In general, the hormone is discontinued by the fifth to fourteenth day, rather than after three weeks, as has been advocated by Russek (1). In 2 patients, paretic symptoms returned shortly after discontinuation of steroid therapy, and accordingly treatment was resumed for several more weeks. One patient with pseudobulbar palsy experienced several such "rebound phenomena." He successfully took the medication orally for several months before discontinuing it, notwithstanding my concern about a greatly enlarged and previously decompensated arteriosclerotic heart, for which he was receiving digitalis and mercurials.

Complications

One is reluctant to administer adrenocortical steroids in a case of stroke, as more often than not the patient has a hypertensive, nephrosclerotic or diabetic background. Fortunately, to date we have witnessed no serious complications on this account. There has been no sodium-retention edema, nor have we observed thromboembolism and deterioration of myocardial efficiency in patients with previous or coexisting heart failure. Perhaps the absence of side-effects has been due to the relatively short duration of therapy.

The patients with xanthelasma, or with levels of serum cholesterol that were either elevated or borderline, were closely observed for thrombotic phenomena in the vessels of the heart, lungs and legs. These complications are known to occur following the administration of cortisone or corticotropin in the presence of hypercholesterolemia (15), but were not noted in this particular series of cases.

In Case 5 there appeared to be no delay in the healing of the extensive subendocardial infarction that was associated with the severe injury to the brain stem. It is of some interest in this regard that upon administering adrenocortical steroids in full dosage to patients with acute myocardial infarction, we have not observed any complications. (These patients had experienced severe exacerbations of a previous rheumatoid arthritis or gout shortly after being hospitalized. Pain was not ameliorated even by opiates, and consequently they were so restless that the risk of complications resulting from the use of adrenocortical hormones was regarded as less than that resulting from their excessive activity.)

One male patient (not reported here) who had suffered a cerebral infarction six weeks prior to the institution of oral prednisolone therapy also improved temporarily. However, persistent epigastric distress developed, which was not benefited by antacid therapy. There was no gastro-intestinal bleeding, but the hormone was discontinued under the circumstances. In 2 female patients, concomitant chronic and recurrent urinary-tract infections were successfully treated with sulfonamides and nitrofurantoin. The intense nondiabetic polyuria in Case 9 was an unanticipated complication that proved too much for his nursing personnel to cope with. In this series there were no seizures that could be attributed to steroid therapy.

Relationship of adrenocortical steroids to other modes of therapy

All the patients in this series were advised concerning salt restriction, adequate hydration, supplementary vitamin therapy, and between-meal ingestion of milk or antacids. Many were given potassium chloride. Most of them also received parenteral vitamin B_{12} and oral nicotinic acid or a niacin-pentylenetetrazol combination (Nicozol). In all severe cases the patients were placed in an oxygen tent for at least forty-eight hours, after insuring that an adequate airway had been established and maintained. The amount of oxygen which patients receive in this manner is not often of sufficient magnitude to induce significant vasoconstriction and a decrease in cerebral blood flow. Since pulmonary edema and aspiration pneumonitis not infrequently complicate the clinical picture (16), antibiotic therapy was used temporarily in these instances. (It is conceded that

on occasion "prophylactic" antibiotic therapy may not only be without value, but may actually be the basis of further infectious complications.) Physiotherapy and psychotherapy were instituted as soon as possible in all cases; their beneficial effects were unquestionably facilitated by hormonal therapy (3).

There were several additional conservative measures that may possibly have contributed favorably to the convalescence of these patients with acute or subacute strokes. Zoxazolamine (Flexin) is at times of great value in reducing the spasticity observed in cases of hemiplegia. The administration of autogenous carbon dioxide by means of breathing into, and out of, a paper bag for fifteen to thirty seconds may alleviate recurrent episodes of focal cerebral anoxemia, presumably by reducing angiospasm (17). I have not been impressed with the effects of papaverine hydrochloride, although Russek and Zohman found this drug to be of prophylactic value in oral dosages ranging from 0.3 to 1.2 Gm. daily (18). Although not an entirely innocuous procedure, especially in the elderly, hypothermia (artificial hibernation) and a concomitant negative water balance have been recently reported as favorably influencing cerebral edema (19).

I am a firm advocate of the policy of *noli me tangere* (touch me not) when it comes to the arbitrary use of most *antihypertensive preparations* in the presence of *any* degree of hypertension in patients over 55 years of age. This is particularly true in the case of female patients who have no significant degree of retinopathy and in whom the hypertension has been longstanding and adequately compensated. Since mild hypertension usually represents Nature's way of insuring an adequate head of pressure to perfuse the vital organs through their arteriosclerotic vessels, antihypertensive therapy is not only meddlesome, but potentially very dangerous.

This hazard is in direct proportion to the hypotensive capacities of the drug used. It has been clearly shown that when the "critical closing pressure" is attained under conditions of systemic hypotension or reduced cardiac output, the collateral circulation of a brain in which arterial flow had been previously compromised often becomes inadequate for the metabolic requirements (20). In the course of their studies on the cerebral collateral circulation, Denny-Brown and Meyer (21) recently demonstrated that cerebral infarction may be ultimately produced by ischemic anoxia, but is definitely reversible in its early stages along with the microstasis if the blood pressure can be elevated or supported. In fact, the effective collateral circulation (which is also related to the severity of brain damage) is directly dependent on the systolic pressure. These investigators also pointed out that thrombosis appears to play but a little role in the early stages of obstruction of the cerebral cortical vessels in such ischemic areas.

In my consultation practice, I have observed a number of cases of stroke—especially those involving the vertebral-basilar artery network—which were induced by unnecessarily aggressive antihypertensive therapy. If this be true of patients with non-malignant hypertension who exhibit no evidence of previous cerebrovascular infarction, it is obvious that insult is being added to injury when the latter has already taken place (22). Mention should be made of 2 additional pertinent facts: 1) even the physiologic reduction of the blood pressure during

sleep poses a constant threat to these patients, and 2) it has been conclusively shown (both clinically and by electroencephalographic studies made in the course of lowering the blood pressure by means of a tilt table) that in cases of moderate hypertension with obliterative disease of the carotid or basilar arteries, cerebral insufficiency can be repeatedly induced with a *minimum* systolic blood pressure of 160 mm. Hg (23). This problem is unfortunately becoming greater with the passage of time, as more and more powerful hypotensive drugs are being released. Such agents as histamine and nicotinic acid must also be administered with some degree of caution in order to avoid excessive drops in systemic blood pressure.

On the other hand, hypotensive agents may be indicated in the treatment of the younger patient with malignant hypertension who has a cerebral or subarachnoid hemorrhage and whose condition is deteriorating in the presence of a high diastolic blood pressure (24). It should be emphasized, however, that high elevations of blood pressure are not unusual during the course of acute intracranial bleeding in patients with no evidence of pre-existing hypertension.

The subject of the advantages of stellate ganglion block and of anticoagulant therapy frequently arises in the management of the patient with acute hemiplegia or the moribund patient with stroke. There are usually no objections to performing a *stellate ganglion block*, which is a relatively safe and easy procedure in experienced hands. It induces temporary inhibition of the intracranial autonomic sympathetic inflow. Should a dramatically beneficial result ensue—as is the case in 3 to 5 per cent of these patients—the treatment has obviously been justified. On the other hand, some observers feel that this procedure is actually detrimental in certain cases of cerebral infarction (25).

The clinician must be mindful of the fact that a stellate ganglion block can do nothing more than relieve vasospasm of either the major arteries or the small vessels on the periphery of a small cerebral infarct, particularly after a cerebral embolus. It does *not* increase the total cerebral blood flow (26). (The rebreathing of autogenous carbon dioxide by means of a paper bag, or the addition of 5 to 7 per cent carbon dioxide to oxygen inhaled by mask may be temporarily helpful in these instances because of increased cerebral blood flow (17, 27)).

In the use of *anticoagulant therapy* for acute cerebrovascular accidents, on the other hand, one is faced with more serious considerations. The presence of blood in the spinal fluid contraindicates this form of treatment. However, in early cases there may be an intracerebral clot that has not had time to rupture into the ventricular system; in such an instance there would be no blood in the spinal fluid.

Furthermore, even in the presence of cerebral infarction, there is the definite risk of converting an anemic lesion into a hemorrhagic one. A related reservation is raised in the case of cerebral embolism, because of the high frequency of associated hemorrhagic cerebral infarction. This is in contrast with the rare occurrence of hemorrhagic infarction in association with cerebral thrombosis. Sibley and his colleagues (28) clearly demonstrated the decidedly increased risk of aggravating these hemorrhagic infarctions in their studies on experimentally

produced emboligenic infarcts in the brains of dogs. It is because of these implications that I feel more justified in advocating parenteral cortisone as the preferred type of heroic therapy in the patient with a probable massive cerebral infarction at the present time.

Anticoagulant therapy can always be kept in reserve to use later, particularly when there is the likelihood of embolism originating from a rheumatic heart or myocardial infarction (29). (Even under these circumstances, therapy with cortisone has been successful (30).)

Under my care are several hypertensive patients who have had recurrent bouts of "cerebral vascular insufficiency" of serious proportions, involving the basilar or internal carotid artery networks. Long-term dicoumarol therapy has allowed them comfort and clarity of mental activity for extended periods. This experience coincides with that of Millikan and others (31). One 52-year-old businessman who has been receiving this drug for over a year, repeatedly experiences a numbness of his right hand when the medication is omitted or the hypoprothrombinemic effect is lessened. It is the general consensus that the anticoagulant drugs act not only by disintegrating existing thrombi, but also by preventing propagation of the original thrombus and by preventing the development of intracranial and other thrombi (29).

Problems in diagnosis

Several facts concerning the diagnosis of cerebral infarction are not sufficiently appreciated, especially when one considers that cerebrovascular accidents are the third most common cause of nontraumatic death in our country. The many perplexing clinical syndromes which may result from "little strokes" affecting the "silent areas" of the brain have become increasingly recognized and will not be belabored here (32).

Such is not the case, however, with *thrombosis of the anterior or posterior inferior cerebellar artery* (resulting at times in the syndrome of Wallenberg) and *thrombosis of the vertebral and basilar arteries*. The brain stem appears to be able to weather this induced ischemia more effectively than was previously thought possible (8). It is because of this fact that prompt adrenocortical steroid therapy may prove to be uniquely beneficial in these conditions. Although only 2 of the patients with acute cerebral accidents reported here (Cases 7 and 8) exhibited the typical features of these syndromes, it must be borne in mind that there is such marked lability of neurologic signs in the acute phase that it often precludes specific anatomic localization (11).

It is becoming increasingly clear that occlusions of the cerebellar artery, the vertebral artery, and the internal or common carotid arteries are frequently the cause of acute spontaneous cerebrovascular accidents in normotensive adults under the age of 40 years. Studies of several large series of such patients stress the fact that premature arteriosclerotic vascular changes constitute the most common pathogenetic factor in this situation, as is the case in coronary occlusion affecting the young (33, 34). Many physicians are reluctant to accept this explanation for focal cerebral signs, even after ruling out the presence of such

conditions as neoplasms, vascular anomalies, subdural hematomas, fat embolism, diffuse arteritis, collagen disorders, syphilis, hematologic disorders, and intracranial venous thrombosis or thrombophlebitis.

A tentative diagnosis of a *carotid artery occlusion* sometimes can be made, without angiography, on the basis of inability to palpate the internal carotid pulse in the posterolateral pharynx (35), measurement of retinal artery pressure (36), or by precipitation of unconsciousness when the opposite carotid artery is temporarily occluded. It is quite likely that the reported cases of hemiplegia following carotid sinus manipulation have been in patients who had previously had advanced and unrecognized carotid artery insufficiency. The combination of homolateral blindness and contralateral hemiplegia should suggest extracranial occlusion of the internal carotid artery with concomitant involvement of the ophthalmic artery (37). The occlusion may be manifested primarily by "senile dementia." Patients with involvement of the basilar and carotid arterial systems exhibit a striking liability to marked falls in blood pressure incident to changes in posture. This must be kept in mind when recurrent dizziness, vertigo, "Ménière's syndrome," syncope, changes in vision, ataxia, dysarthria, and confusion ensue after postural changes (38).

The diagnosis of *intracerebral hematoma* is made much too frequently instead of a diagnosis of *cerebral infarction*. Neurosurgical intervention usually should be withheld until the complete syndrome appears. This train of events consists of: 1) evidence of an initial brain hemorrhage, with coma or stupor; 2) restoration of consciousness in the presence of lateral neurologic signs; and 3) subsequent loss of alert behavior associated with the manifestations of increasing intracranial pressure. In an occasional case of this kind, evacuation of the clot has been beneficial (39, 40).

A number of cases of infarction and encephalomalacia have been reported in which the clinical symptoms and signs of an expanding intracranial lesion caused the surgeon to explore the region primarily for a brain tumor (41). *Occlusions of the vertebral or cerebellar arteries* have simulated *tumors of the posterior fossa*, both clinically and radiographically. The increased intracranial pressure is presumably a result of cerebellar or medullary softening with subsequent compression and dislocation of the aqueduct and the fourth ventricle (42). Unfortunately, the initial hope that elevation of the level of the enzyme, glutamic oxalacetic transaminase, in the cerebrospinal fluid would aid in differentiating cerebral infarctions from cerebral tumors and other neurologic disorders has not been fulfilled (43).

A final comment is in order concerning *pseudotumor cerebri* in view of the fact that most clinicians are not familiar with this entity and its relatively good prognosis, and that it may prove to be susceptible to steroid therapy. Pseudotumor cerebri is characterized by signs of increased intracranial pressure (elevated cerebrospinal fluid pressure, headache, vomiting and papilledema), minimal or no abnormal neurologic signs (lateral rectus palsy and diplopia are the most frequent findings), a normal spinal fluid, and a normal or small ventricular system as shown by pneumoventriculography (44, 45). This disorder is

most frequently found among women under the age of 30. It apparently results from transient vasomotor changes and associated cerebral edema. Accordingly, there might be a dramatic and possibly a diagnostic response, not only to restriction of fluid and salt but also to adrenocortical steroid therapy, thus obviating neurosurgical exploration and decompression. The author is not aware of any such reports at the present time.

SUMMARY

Adrenocortical steroids are of great value as adjunctive therapy in the management of certain seriously-ill patients suffering from acute or subacute cerebrovascular accidents. There are many objections to be met when proposing any therapeutic agent for treatment of strokes. Whenever possible, in our series, remissions of a spontaneous nature or due to other forms of treatment were ruled out by varying periods of observation prior to the institution of hormonal therapy.

The use of adrenocortical steroids apparently was a life-saving measure in a number of critically-ill patients with cerebral infarction who were not expected to survive. Nine case reports are presented. The beneficial effect was particularly striking in cases of severe involvement of the brain stem. Alleviation of stupor, depression, apathy, paralysis, impaired deglutition, and clouded consciousness was frequently dramatic within twelve to twenty-four hours.

Short-term supportive steroid therapy was of considerable value in the rehabilitation of other patients with persistent hemiplegia or pseudobulbar palsy.

An analysis is presented of the rationale for such therapy, the potential complications, and the relationship to other measures in the treatment of cerebrovascular accidents. It is emphasized that there should be no indiscriminate use of adrenocortical steroids in the treatment of stroke.

Pertinent features relating to important but little-appreciated aspects of the diagnosis of stroke are briefly reviewed.

It is hoped that others will be encouraged to study this form of therapy and report their experiences. If the beneficial effect is confirmed, adrenocortical steroids may prove to be of great value in improving the plight of certain seriously-ill patients suffering from massive strokes.

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Editorial

GERIATRIC RESEARCH

"Geriatric Research" is a term heard more and more frequently as the enormous importance of geriatric problems becomes more and more vivid. These problems abound in economic, social, legislative, housing, medical and other areas. Research can be found in all of them, and the adjective "geriatric" can be applied to it in any field concerned with the welfare and well-being of the elderly. In most areas, the definition is clear-cut and beyond reasonable question but this is not the case when the term "geriatric" is applied to investigations conducted within the realm of medicine. Despite this fact, there is remarkable uniformity of thought on the subject. It is the dearth of attempts at definition which accounts in part for the fluid phase of the definition; and the apparent reason for the dearth is that any definition must be so comprehensive that it seems not worth the effort to most investigators.

There is another reason, too, for the continued looseness of the term in medicine. This is the weight carried by the few dissenters—those who hold that growth and maturation are logically a part of aging. Chronologically speaking, they are right and may be right in other ways as well. However, if any investigation in which time is a factor were to be called "geriatric research" the term would be worse than useless, as there is nothing which it would not encompass. It seems worthwhile, therefore, to place some arbitrary limit on the definition of the term. This paper is an attempt to do so, and it also contains a suggestion for one important direction that such research might take, following a pediatric lead.

The definition referred to is one which is beginning to prove itself useful in the Veterans Administration. Here Geriatric Research is considered to be the investigation of any aspect of any physiologic or psychologic deterioration which is common in old age and, as a rule, thought to be due to old age. The bases for these deteriorations are sometimes detectable while they exist as symptomless, simple, although retrograde, changes. The age at which they can be found is not considered; it is only their retrogressive nature that is important.

Growth and maturation are normal functions and are not retrogressive, as is made clear by the study of cells. Growth of a person, an organ, or a tissue is the result of expansion and subsequent division of the cells. There, expansion and contraction alternate rhythmically. The former is the equivalent of growth; the latter, of maturation. Growth and consolidation of that growth do not take place simultaneously; rather, one phase alternates with the other and the two together constitute normal life for the cell.

Each cell has a fixed life-time. Each is born and dies like a member of a community, with the community itself persisting. Cells in the blood today are not the ones of last year and not even entirely those of yesterday; yet the blood goes on, unchanged in general quality. In tissues and organs, cells must change too, but here the cells are not as independent as those in the blood. In the tissues they work together on a specific project and the project itself (*e.g.*, a cartilaginous epiphysis or the thymus) has greater phases of growth and maturation than those of any single cell. The project, though, may have a termination date

which is distinctly earlier than that of the community—in this case, the man. The cartilage cells in the epiphysis complete their work at various early stages of life and in each location they, in effect, retire en bloc. In the thymus the same is true. Individual cells live and die, even if organized. The separate projects are subjugated to the good of the community.

Cells, tissues, organs and man are related as though through a system of harmonics. The pattern of cellular activity is repeated on a longer and longer swing, just as the rhythmic alternation of warmth and coolness is recognizable on a daily basis, then in a seasonal or yearly pattern, and in still longer cycles. This rhythmic alternation is the pattern of life.

The cell is related to the man as the man is to humanity, and their characteristics are similarly related. Those of the cell vary with its phase. The expanded cell is more permeable to substances passing into or out of it, and it is less electrically conductive than is the contracted cell. In the man, the situation is parallel. During the expansile phase of the individual he, like the cell, is permeable. His permeability includes facts and fancies, as well as a variety of diseases so common during growth that they are grouped popularly as "childhood" diseases. In his inactive, or contraction phase, these characteristics change in man as in the cell. His electrical conductivity now is increased or, to put it physiologically, his nervous system can carry its messages more readily over established tracts and relate them properly. His reactions are no longer the short reflex motor responses which are dominant in infancy. In the vernacular of chemistry, his indiscriminate absorption has become more specific.

This is the normal. During the normal 2 phases in any individual, new cells are continually being formed to take the place of others which, having lived their normal, shorter lives, have deteriorated and have been discarded. This process must be regarded from the point of view of the whole person, the community, which profits from its components only as long as they contribute. The shedding of deteriorated cells or the cessation of an organ (like the thymus) which is no longer required, is not deterioration. Deteriorations are alterations which are detrimental to the individual, even though some of the affected cells become fat in the process.

Prolongation of the growth and maturation phases would be a utopian objective for Geriatric Research. More realistically, Geriatric Research should strive to find ways of keeping in stable balance with each other those physiologic and psychologic functions which go hand in hand under normal circumstances. The upset of one may be reflected in an upset of the other, even to the degree in some instances that the latter may be the cause of greatest concern; for example, senile dementia may be the presenting chief complaint, whereas vascular impermeability may be the cause.

The growth or expansile phase of the individual does not end with the establishment of sexual "maturity" (puberty), nor is the end of the maturation or contraction phase synchronized with the sexual change called the menopause. The "sex" hormones are detectable in embryos within a few months of conception, at a time when the amplitude of their rhythm is small indeed and the internodal periods relatively long. In the infant, the amplitude is increased and

the phase somewhat shortened. As the child grows, the hormonal levels rise and a periodicity becomes evident. At puberty these levels have become high enough to affect the development of the sex organs conspicuously and the phase is established as a "menstrual" month. After a long stage of maturity during which the periods remain grossly regular, there is a return in old age to longer swings of lower amplitude. This takes place gradually and rhythmically.

The hormones which best demonstrate this rhythmic action are known as sex hormones, because it is on the sexual organs that their effect is most apparent. Most hormones affect the psychologic outlook and many of the physiologic functions in both sexes, but the sex hormones have been the most studied in this respect. The activities referred to are entirely apart from those thought of as reproductive. These include the control of cellular permeability and, by this means, the admission or non-admission of infective organisms by way of the lung to the body. This was conclusively demonstrated years ago by Lurie. He observed the influence of sex hormones on "spread," a phenomenon regulated by the state of the intercellular cement substance. This substance is found throughout the body, for example in the sclerae, in the parts involved in collagen diseases, in the skin and, importantly, in the walls of blood vessels and the sheaths of nerves. Since blood must reach every cell, and since all of the cellular components reach the blood and leave it again through an intact wall, the permeability and general state of health of the vascular walls have much to do with the efficiency of all body function. The same can be said of the nerves. Each fasciculus, as well as the whole nerve, is bound in connective tissue. Intercellular cement is an important constituent of this connective tissue, and through it oxygen and all nutriment must pass to reach the cell.

Sex hormones seem as important in their effect on intercellular cement substance as in the command of reproduction—a function assigned to them long ago. But what portion of reproduction can be separated from the mind and the body as a whole? The absorption of oxygen and nutriments, urinary excretion, and other physiologic functions are as essential to reproduction as are genes and genitalia; and mental attitudes are not excluded from the process. Clearly sex, psyche and soma constitute a triad, all controlled centrally through neurohormonal means, and all act together as if enmeshed like gears. No component of this triad can be considered autonomous.

These close relationships make correlation a logical and practical approach to the study of man at any age, and this has been used to great advantage in pediatrics—though sometimes unwittingly. In pediatrics the large body of information makes many such correlations appear to be just ancient common knowledge. Observations on children are automatically related to age. In later life the relationship is not so distinct, and so associated phenomena must be recognized and correlated. The reason for the close tie-in with age in the pediatric period is obvious. Since the time between birth and puberty is short compared to that between maturity and senescence, the normal physiologic changes in childhood have less latitude for variation in the time of onset. When one speaks of an infant of 3 months, for example, the physiologic pattern is implied. One infers that this infant has immunity to measles, that he is highly susceptible to strepto-

coccal infection, that a few carpal epiphyseal centers are present, that his blood shows a relative lymphocytosis, that his appetite is prodigious, that he is gaining weight and is lethargic most of the twenty-four hours, and that his cells are dividing at a very rapid rate. The age of a child conveys these and other thoughts to the pediatrician without his being consciously aware of the correlations.

At 2 years of age the infant is susceptible to measles and is becoming susceptible to mumps and typhoid. He is becoming resistant to tuberculosis but is still highly vulnerable to the streptococcus. His differential blood cell count has changed somewhat toward the adult pattern. His appetite is small and is of great concern to his mother. He is no longer the fat baby and he may acquire diseases such as generalized herpes simplex or nephrosis, to which he will again become less vulnerable when he reaches the age of 5.

The coexistence of certain physiologic states, psychologic outlooks and clearly defined susceptibilities and resistances is to be found at all stages of childhood. It seems that when there is a change in any one of these, it is reflected in the others. Undoubtedly, this is the result of the over-all central control exerting its influence through the nervous system and hormones.

At the other end of life, however, a person's age tells us little. There is no such precise correlation of age with changes in blood, bone, nerve or other tissues, as is the case in childhood. A man of 50 years and one of 70 years may be similar physiologically, yet the difference in their ages is much greater than the entire time from birth to puberty. On this account, it is apparent that it is meaningless to express physiologic observations in terms of age. However, it is equally evident that various physiologic functions at all stages of life are correlated with one other and with the psychologic status.

Relationships similar to those in childhood must exist in later life. It should be possible, on discovery of a regular concomitant in one area, to deduce the status of the other processes in other areas. This would include abnormal conditions as well as normal ones. For example, during the time that cell division and growth are most rapid in early life, the white blood cell picture is distinctive, calcification of bone is relatively slow, and sleep comes easily. These and other manifestations are accompaniments of development during the normal growth period. Is it not possible that rapid growth which is abnormal in time, type or location, has regular concomitants too?

Detection of deterioration in its earliest stages, even before it can be accurately labelled as such, may make it possible to reverse the process by such simple measures as diet or hormones. Research into possible sites of reversible change must extend from the molecular through clinical and psychologic levels. Prevention of deterioration is not prevention of chronologic aging but, if it can be accomplished, will prolong the period during which the individual can be a contributing member of society.

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Abstracts of Current Literature

AGE DIFFERENCES IN CHOLINESTERASE ACTIVITY OF SERUM AND LIVER.
Barrows, C. H., Jr.; Shock, N. W., and Chow, B. F. *J. Gerontol.* **13:** 20 (Jan.) 1958.

A study was undertaken to determine whether alterations in enzymic activities of the blood occur with advancing age. Serum cholinesterase determinations made in 128 men between the ages of 20 and 90 years showed a significant decrease in the concentration of the enzyme with age. No cholinesterase activity was present in the urine of men over 70 years of age, so that the change in concentration of serum cholinesterase with age could not be attributed to loss through the urine. Cholinesterase activity in the serum of female rats 24 to 27 months old was significantly lower than that in rats of the same sex 12 to 14 months of age. No differences were apparent in the cholinesterase concentrations in liver tissue from young and old female rats.

SODIUM INTAKE OF THE AMERICAN MALE: IMPLICATIONS ON THE ETIOLOGY OF ESSENTIAL HYPERTENSION.
Dahl, L. K. *Am. J. Clin. Nutrition* **6:** 1 (Jan.–Feb.) 1958.

Evidence that the level of sodium intake is the primary etiologic factor in the development of essential hypertension in human beings led to the determination of the sodium intake of a group of ambulatory asymptomatic American adults in order to have a baseline for comparison with the sodium intake of persons in other lands in whom hypertension is present to a greater or lesser extent than in persons in America. The urinary excretion of sodium was measured in 71 adult males. Twenty-two of these men had asymptomatic essential hypertension of varying levels. It was assumed that the urinary excretion of sodium was equivalent to the sodium intake. No conditions that would invalidate this assumption were present in the persons studied. Twenty-four hour urine collections were made for periods ranging from one to thirty-eight days. The average and median levels of daily urinary sodium excretion, determined by single collections and by multiple collections in 28 subjects, were about 180 mEq./day, or the equivalent of 10 Gm. of sodium chloride per day. The range was 63 to 406 mEq./day, or the equivalent of 4 to 24 Gm. of sodium chloride, respectively. Studies are cited which show that hypertension is virtually absent among primitive peoples who have in common a low intake of sodium. On the other hand, the incidence is high among West Indian negroes who have a high intake of sodium even from early childhood because of a diet of salt pork and fish.

THE USE OF PACATAL WITH AMBULATORY PATIENTS IN GENERAL PRACTICE.
Darlington, H. F. *Pennsylvania M. J.* **61:** 207 (Feb.) 1958.

Pacatal, a phenothiazine derivative, was administered to 50 patients with deep-seated feelings of anxiety, tension, and inadequacy. The diagnoses among them were: arteriosclerotic heart disease, coronary angina, menopausal syndrome, duodenal ulcer, spastic colitis, migraine headache, or senile psychosis. The majority were in the sixth or seventh decade of life. All sedatives and ataractic drugs were discontinued and each patient was given an initial dosage of 25 mg. of Pacatal three times daily in order to evaluate the response. A daily dosage of 100 to 150 mg. usually proved adequate. A sedative, or meprobamate was sometimes prescribed at bedtime for insomnia but, in general, the need for sedatives was reduced. Pacatal induced a more nearly normal response to emotional stimuli without producing a sedative or lethargic effect, especially in elderly irascible patients.

They became more optimistic, cheerful, and cooperative. Both older and younger patients experienced significant relief of anxiety, tension, and depression. Elderly patients became better able to cope with daily problems and frustrations. Particularly good results were obtained when Pacatal was used to supplement the action of coronary vasodilating agents, antacids, and antispasmodics. This beneficial action is attributed, not to synergism but to the normalizing influence of Pacatal upon the patients' mental state.

EXPERIMENTAL HORMONAL THERAPY OF ATHEROSCLEROSIS: PRELIMINARY OBSERVATIONS ON THE EFFECTS OF TWO NEW COMPOUNDS.

Davis, F. W., Jr.; Scarborough, W. R.; Mason, R. E.; Singewald, M. L., and Baker, B. M., Jr. *Am. J. M. Sc.* **235:** 50 (Jan.) 1958.

Two new compounds, developed in a search for substances capable of producing favorable changes in plasma lipoprotein distribution without inordinate feminization, were tested in 61 patients (47 men and 14 women) with atherosclerosis who had myocardial infarction or angina pectoris, or both, and in several instances had severe peripheral vascular disease as well. Twenty-three patients received SC-4289, a nonsteroidal synthetic compound, for an average of 9.8 months; clinical improvement occurred in 65 per cent. Most of them experienced a sense of well being and relief of anginal pain. No feminization occurred. Objective studies showed improvement in the following in the percentages of patients: electrocardiogram, 21.7; ballistocardiogram, 43.5; a less marked ballistocardiographic reaction to smoking, 35.3. The total cholesterol level decreased in 26.1 per cent but increased in 34.8 per cent so that no significant change appeared to result from administration of the drug. In general, electrophoretic patterns showed an increase in the fraction of lipoprotein in the beta zone. Twenty-seven patients received Manvene (SC-6924), a synthetic oil-soluble crystalline powder, for an average of 7.3 months. Although 73 per cent of the patients noted a decrease in anginal pain, the sense of well being provided by the former compound was not noted. The ballistocardiogram, the smoking test, and the serum cholesterol level were influenced in a manner similar to that with SC-4289. A fall in the concentration of serum total cholesterol occurred in 20 per cent. In contrast, 65 per cent of the patients showed a favorable shift in beta lipoproteins to, or toward normal. Fifteen per cent showed the opposite change. Minimal to moderate soreness of the breast and enlargement occurred in 55 per cent of the patients and necessitated withdrawal of the drug in one of them. Two men had complete loss of potentia. Uterine bleeding in 2 women required that the dosage be reduced, and gastro-intestinal symptoms in 1 patient prohibited adequate dosage. Among 11 patients receiving massive dosages of estrogens for an average of fourteen months, 82 per cent improved subjectively. The ballistocardiogram improved in all patients. Sixty per cent showed less deterioration in the ballistocardiogram in the smoking test. A fall in the serum cholesterol level to normal occurred in 60 per cent (the remaining values were normal during the control period). The beta lipoproteins were normal in half of the patients during the control period and fell to normal during estrogen therapy in the remainder. The mean fall in cholesterol concentration was 86 mg. per 100 ml. It is concluded that the use of Manvene offers an opportunity for extended therapy in a quantity sufficient to influence serum lipids favorably without prohibitive feminization. Such usage is in an experimental stage and cannot as yet be applied indiscriminately in the treatment of patients with coronary atherosclerosis.

THE INFLUENCE OF ANDROGENS, ESTROGENS, AND RELATED STEROIDS ON SERUM LIPIDS AND LIPOPROTEINS. OBSERVATIONS IN HYPOGONADAL AND NORMAL HUMAN SUBJECTS.

Furman, R. H.; Howard, R. P.; Norcia, L. N., and Keaty, E. C. *Am. J. Med.* **24:** 80 (Jan.) 1958.

Data representative of a four-year study of the influence of gonadal steroids on serum lipids and lipoproteins in more than 60 human subjects are presented. Estrogens promptly

and consistently increase high density $-S_{1.21}$ 0–12 (alpha) lipoprotein concentrations, whereas androgens promptly lower them. The concentration of lower density $-S_{1.21}$ 25–40 (beta) or $-S_{1.21}$ 25–70 lipoproteins characteristically either does not change, or changes in a direction opposite to that of the high density lipoproteins, when gonadal steroids are administered. The response of the chemically determined serum cholesterol and phospholipid concentrations may be predicted on the basis of the lipoprotein changes induced by gonadal steroids in individual subjects. When the concentrations of high density and lower density lipoprotein fractions change in opposite directions, serum cholesterol and phospholipid levels show little or no change. When lower density lipoprotein concentrations fail to change following gonadal steroid exhibition, then serum cholesterol and phospholipid levels change in the same direction as that of the high density lipoproteins. Serum phospholipid levels tend to vary with the high density lipoprotein concentrations more than does the serum cholesterol level, presumably because of the relatively high phospholipid/cholesterol ratio of the $-S_{1.21}$ 0–12 lipoproteins. Changes induced in the serum lipoproteins by gonadal steroids tend to persist for one or more weeks after therapy is discontinued and after nitrogen balance has returned to the control state. No "wearing off" phenomena have been observed. The responses of the lipoproteins do not appear to be conditioned by urinary gonadotropin or 17-ketosteroid excretion, and may be elicited in hypothyroidism and panhypopituitarism. The changes induced in the serum lipoproteins of human subjects by gonadal steroid administration suggest that the relative immunity of women to coronary atherosclerosis may be attributable either to relatively large concentrations of high density lipoproteins or to relatively high values for high density-lower density lipoprotein ratios. The data also indicate the necessity of study of the entire serum lipoprotein spectrum if the physiologic or etiologic importance of these lipoproteins in health and disease is to be fully evaluated. (From authors' summary and conclusions.)

OSTEOPOROSIS IN THE AGED: RADIOGRAPHIC SURVEY WITH CLINICAL AND BIOCHEMICAL CORRELATIONS.

Gitman, L.; Kamholtz, T., and Levine, J. *J. Gerontol.* **13:** 43 (Jan.) 1958.

Among 565 institutionalized elderly subjects, the incidence of radiographic osteoporosis was higher in females than in males in all age groups above 65 years. The sex difference was marked among those patients with significant osteoporosis, in that there was a threefold increase in females as compared to males. In females, the incidence increases markedly with age, but it remains stationary in males. The state of ambulation seemed to be only indistinctly related to the degree of osteoporosis, so that the absence of physical activity appears to play only a minor role in the pathogenesis of osteoporosis in the aged. No correlation could be found between the degree of osteoporosis and the incidence of back pain, nor was there any correlation with body weight, hemoglobin, blood levels of calcium, phosphorus, alkaline and acid phosphatase, sugar, urea nitrogen, total protein, albumin, globulin, and vitamin A, vitamin A tolerance curves, or thyroidal uptake of radioactive iodine.

THE RESULTS OF TREATMENT OF PSYCHOTIC STATES WITH NEWER PHENOTHIAZINE COMPOUNDS EFFECTIVE IN SMALL DOSES.

Goldman, D. *Am. J. M. Sc.* **235:** 67 (Jan.) 1958.

Four phenothiazine compounds were investigated in the treatment of chronic psychoses in patients confined to a mental hospital. These were Compazine, 667 patients; Trilafon 206 patients; Vesprin, 176 patients; and Winthrop #13,645-5, 94 patients. In comparison with previously familiar phenothiazine derivatives such as chlorpromazine, these substances possess more intense pharmacologic and therapeutic activity, can be used in smaller dosage, and are much less likely to cause side-effects and toxic complications. The majority of the patients received the following daily dosages: Compazine, less than 150 mg.; Trilafon, less than 65 mg.; Vesprin, less than 300 mg.; Winthrop 13,645-5, less than 150 mg. These drugs proved particularly effective in the treatment of schizophrenia, manic depressive psychoses in the manic group and synergistically with electroshock in the depressed group,

and organic delirium. As compared with chlorpromazine and reserpine, these drugs had a greater beneficial effect on psychotic manifestations such as delusions, hallucinations, and pathologic excitement. Increasing proportions of good results were obtained as the duration of therapy lengthened. Prolonged administration was not found to increase the likelihood of severe or serious toxic manifestations, as these were prone to occur within the first eight to twelve weeks, if at all. Moderate improvement also occurred to a significant degree and made it possible to eliminate practically all restraints and "deteriorated" wards. In this study: 1) no severe toxic effects, no jaundice, and no agranulocytosis were produced, 2) in comparison with earlier phenothiazine drugs, the allergy-like manifestations were less frequent in the usual dosage range (a slow rate of increase in dosage may have reduced the possibility of severe toxic effects) and the trophic and endocrine effects resembled those of chlorpromazine but were likely to be milder, 3) the chief neurologic effect, the production of parkinsonism, came to be regarded as a necessary accompaniment of therapeutic benefit in some cases that should be managed by manipulation of dosage and the administration of Cogentin, 4) somnolence and sedation were not produced, so that patients were easier to handle and ready sooner for efforts at rehabilitation, and 5) the principal effect of drug therapy in psychoses was found to be resolution of a disorder in control of perceptive processes. Compazine in comparison with Trilafon was 1) apparently equal and similar in effect, 2) more stimulating, 3) less likely to produce a minor degree of somnolence in its early use, and 4) more likely to produce turbulence of clinical importance. Trilafon produced parkinsonism with smaller doses and more quickly. Vesprin 1) proved milder in the production of side-effects than Compazine or Trilafon, 2) produced less parkinsonism, probably because of conservative dosage, 3) did not cause turbulence, and 4) produced more side-effects when the dosage range was increased. Winthrop 13,645-5 1) had intense pharmacologic effects on psychotic manifestations, 2) tended to produce sedation without actual influence on the level of consciousness, and 3) produced hypotension similar to that with, but less frequently than, chlorpromazine.

AORTIC STENOSIS OF NO PHYSIOLOGIC SIGNIFICANCE.

Hancock, E. W.; Madison, W. M., Jr.; Proctor, M. H.; Abelmann, W. H., and Starkey, G. W. B. *New England J. Med.* **258:** 305 (Feb. 13) 1958.

Seven patients are discussed who had clinical evidence of aortic stenosis and who were seriously considered candidates for aortic-valve surgery, but who were shown not to have significant narrowing of the aortic valve. This conclusion was based on results of catheterization of the left side of the heart in 5 patients and postmortem examination in 2 others. Each patient presented several of the features characteristic of aortic stenosis. Yet the clinical picture in each was in some respect atypical. The patients actually had, in 5 cases, coronary artery disease with myocardial infarction and, in 2 cases, mitral valve disease not clearly apparent from clinical findings. Cardiac catheterization was of great value in establishing the correct diagnosis and in avoiding ill advised surgery in these patients. Aortic stenosis and chronic coronary artery disease may cause similar clinical syndromes of cardiac disease. Functionally insignificant pathologic changes in the aortic valve may produce clinical signs indistinguishable from those produced by severe aortic stenosis. Thus, patients with signs and symptoms suggestive of severe aortic stenosis may in fact be suffering predominantly from coronary artery disease. The presence or absence of significant aortic stenosis is objectively established by the findings of catheterization of the left side of the heart. This procedure is indicated whenever surgery of aortic stenosis is under consideration and there is uncertainty about the degree of aortic stenosis present. (From authors' summary and conclusions.)

CAROTID BODY TUMORS: A REPORT OF THREE CASES.

Hollenberg, H. G., and Jones, R. D. *Am. Surgeon* **24:** 3 (Jan.) 1958.

The successful removal of a benign neoplasm of the carotid body in 3 cases is reported. Such tumors, whether large or small, are usually asymptomatic. The surgeon must be aware

that common lesions of the lymph glands, branchial cleft cysts, and the more rare neurogenic tumors of other nerves or of the sympathetic chain may simulate carotid body tumors. Tumors suspected of being in the category of a carotid body tumor should be explored surgically. When one is found to be a carotid body tumor, a careful attempt should be made to remove it without disturbing the continuity of the common carotid and the internal carotid arteries. Rather than disturbing the latter, operation should be abandoned. If its continuity is already disturbed, then one of the newer methods of restoring blood flow, such as the use of a homologous arterial transplant, should be used. Following surgery for a carotid body tumor, anticoagulants should be administered beginning two hours postoperatively, in order to prevent thrombosis.

HEMORRHAGIC DIATHESIS RELATED TO QUINIDINE THERAPY.

Hunt, J. C.; Anderson, M. W., and Hanlon, D. G. *Proc. Staff Meet., Mayo Clin.* **33:** 87 (Feb. 19) 1958.

Four cases of purpuric manifestations due to quinidine therapy are reported. In 1 patient, the response to a single dose of 0.2 Gm. of quinidine sulfate resembled an anaphylactic reaction. These cases and the 37 contained in the literature suggest that purpuric or thrombocytopenic reactions, or both, to quinidine occur much more frequently than was once thought. Although such manifestations usually occur in persons who have had a previous exposure to quinidine, they may occasionally occur in persons who have not previously received the drug. Repeated exposure to quinidine with recurrent hemorrhagic manifestations may result in increased severity and suddenness of onset of symptoms. When this occurs, it is hazardous to continue quinidine. The findings are usually those of acute thrombocytopenic purpura. There may be vague premonitory symptoms followed by the insidious development of mild hemorrhagic signs, or the purpura may develop with suddenness and severity. Likewise, there may be a variation from scattered petechiae and ecchymosis to sudden onset of bleeding from multiple sites and systems. The documentation of hypersensitivity to a test dose of quinidine may be hazardous to the patient. When quinidine is discontinued, the prognosis is usually good.

PERIPHERAL NEURITIS ASSOCIATED WITH RHEUMATOID ARTHRITIS.

Irby, R.; Adams, R. A., and Toone, E. C., Jr. *Arthritis & Rheumatism* **1:** 44 (Feb.) 1958 (first issue of a new journal).

Peripheral neuritis has not generally been considered to be a feature of rheumatoid arthritis. Six cases of severe rheumatoid arthritis with development of peripheral neuritis are reported. The average age of the patients was 50 years, and 5 of them were males. All 6 had received cortisone for six months to five years, and prednisone for six months to two years. In 1 patient peripheral neuritis developed during corticotropin therapy. The peripheral neuritis affected the lower extremities in all patients, and the upper extremities as well in 3 patients. It was manifested primarily as a disturbance of sensory components. Numbness, tingling, and burning of the extremities became the patients' chief concern. Careful study showed no other diseases that could have existed to account for the neuritis. Histologic examination of tissue from an amputated extremity of 1 patient together with information gained from the few cases of peripheral neuritis in rheumatoid arthritis previously reported indicate that an inflammatory vascular lesion of the nerve trunk is probably a cause of the peripheral neuritis. It is thought that steroid therapy may play a role, in that it activates a dormant vasculitis. One patient died five years after the onset of peripheral neuritis. The clinical diagnosis was cerebral vascular hemorrhage as part of a diffuse polyarteritis. Five patients are still living ten to twenty-four months after the development of peripheral neuritis, with little improvement in their symptoms. It has not been possible to reduce the maintenance dosage of steroid.

HEXOCYCLIUM METHOSULFATE IN ACTIVE DUODENAL ULCER. EVALUATION OF A NEW ANTICHOLINERGIC DRUG IN CONVENTIONAL AND LONG-ACTING FORMS, ESPECIALLY ITS EFFECT ON GASTRIC pH AS STUDIED IN 48-HOUR ANALYSIS.

Kasich, A. M., and Fein, H. D. *Am. J. Digest. Dis.* **3:** 12 (Jan.) 1958.

In 28 patients with proved active duodenal ulcer, the administration of hexocyclium methosulfate (Tral) in the conventional and in a long-acting form brought about a marked decrease in gastric acidity. The effect was more sustained with the long-acting preparation. Dosages of 100 mg. twice daily suppressed acidity slightly more than dosages of 75 mg. at the same interval. Fifty-seven patients with duodenal ulcer were under treatment with the long-acting form of hexocyclium methosulfate—in a dosage of 75 mg. daily in 24 of them, and 100 mg. twice daily in 33. The duration of therapy varied from less than two months to four months. Ulcer pain and distress were relieved in all, the response being deemed by the patients as better than that with other anticholinergic agents previously administered. In 16 of 20 patients with irritable colon, abdominal cramps and diarrhea, treated with a bland diet and 50 mg. twice daily of the long-acting preparation, cramps ceased and the number of bowel movements diminished. The stools in 10 patients became semi-formed. Constipation developed in 1 patient. No deleterious effects upon the blood, kidney or liver were noted during the administration of hexocyclium methosulfate. The only side-effect was mild dryness of the mouth, reported by the majority of the patients receiving 50 or 75 mg. twice daily.

THE USE OF PREDNISOLONE IN THE TREATMENT OF DISSEMINATED BREAST CARCINOMA.

Kofman, S.; Nagamani, D.; Buenger, R. E., and Taylor, S. G., III. *Cancer* **11:** 226 (Jan.–Feb.) 1958.

Forty-five patients between 27 and 75 years of age with disseminated carcinoma of the breast and with clinically intact adrenal glands, 11 of whom had symptoms of cerebral metastases, were treated with prednisolone. The latter 11 patients received 100 mg. daily and the others 50 mg. daily for three months, unless rapid progression of the disease or side-effects necessitated a change. The criterion of regression was that established by the A.M.A. Subcommittee on Steroids in Carcinoma. Generalized tumor regression occurred in 8 patients. In 3 patients it lasted for more than three months, and in 2 it has continued after one year of therapy. In 5 patients the regression lasted less than two months. Previous castration did not increase the number of regressions. Subjective improvement occurred frequently and was often marked. Therefore, prednisolone is recommended for palliation. Such subjective improvement with the steroid may permit terminal or bedridden patients to receive other therapy. The benefits in some of the patients included such things as improvement in pulmonary symptoms, decrease in hepatic size, increase in appetite, decrease in nausea, decrease in jaundice, or decrease in lymphedema. Clinical improvement occurred in 6 of the 11 patients with cerebral metastases. Regression of the tumor probably occurred in 1 of these patients but the reduction in cerebral edema and inflammatory reaction were probably the mechanisms of benefit in most of the other patients. Lowering of the serum calcium level was noted in 4 of 6 patients with hypercalcemia who received 200 mg. daily of prednisolone; 1 of these had previously undergone hypophysectomy and 1, adrenalectomy. Prednisolone was effective in lowering urinary 17-hydroxysteroid excretion. Changes in 17-ketosteroid excretion following therapy were not statistically significant. In patients who received prednisolone for more than several weeks, there was usually a gain in weight, moon facies, hirsutism, and abnormal fat deposition. Other effects included sleeplessness and nervousness in 2 patients and psychotic symptoms in 2. In 1 of the latter, these symptoms were thought to be due to cerebral metastases. Some diabetes was produced but it could be easily controlled by diet and insulin. Five patients had a gastric or duodenal ulcer during therapy, but ulcer management reduced the frequency of this complication. Quadriceps weakness occurred in several patients.

CHARACTERIZATION OF THE ANEMIA ASSOCIATED WITH CHRONIC RENAL INSUFFICIENCY.

Loge, J. P.; Lange, R. D., and Moore, C. V. *Am. J. Med.* **24:** 4 (Jan.) 1958.

This report describes investigations undertaken to define more precisely the anemia of chronic renal insufficiency and the mechanism of its production. Twenty-six anemic subjects 18 to 71 years of age with chronic renal insufficiency and azotemia formed the basis for this study. The results confirmed that the anemia is normochromic and normocytic. Elevated values for serum iron were not found. Elevated values for free erythrocyte protoporphyrin were found in 8 of 21 patients, but no consistent pattern could be determined. That erythropoietic activity was depressed was shown by decreased ability of the bone marrow to utilize radioactive iron. This depression represents the fundamental cause of the anemia but it is not known whether in uremia patients it results from the toxic action of a retention product on red cell production, or from the lack of a specific erythroid stimulating factor. That an extracorpuscular hemolytic factor is sometimes present was also demonstrated. The hemolytic mechanism is not known. When this factor is present, the anemia becomes rapidly progressive in the absence of detectable blood loss. No intracorpuscular defect was found, but some evidence exists that one may at times be present. The Coombs' test consistently yielded negative results. Abnormal osmotic fragility noted in some patients was probably correlated with the presence of the hemolytic factor, as was the demonstration of an elevated hemolytic index in some patients. The serum bilirubin values remained normal even when there was increased hemolysis. Only 2 patients had significant external loss of blood. Blood loss only occasionally accounts for a significant part of the anemia, but in some cases it may be a third factor.

PREDNISOLONE AEROSOL IN ASTHMATIC BRONCHITIS. A PRELIMINARY REPORT.

Peters, G. A., and Henderson, L. L. *Proc. Staff Meet., Mayo Clin.* **33:** 57 (Feb. 5) 1958.

A 0.5 per cent solution of prednisolone phosphate was used as an aerosol to test its anti-inflammatory effect in 11 asthmatic patients with cough. During each of four to six treatments a day, 0.25 ml. of prednisolone phosphate mixed with 0.25 ml. of 1:200 isopropylarterenol hydrochloride was nebulized during a fifteen-minute period. Water was also used as a diluent, and undiluted prednisolone solution was sometimes used alone. The treatment period ranged from four to twenty-five days. The use of iodide expectorants, ephedrine, and epinephrine by injection as needed, was continued. Ten patients benefited from this treatment. Respiratory irritation diminished and cough subsided. In 1 patient for whom a case report is given, the output of sputum was greatly diminished. Prednisolone phosphate caused no untoward effects. It is believed that this substance as an aerosol may prove useful as an adjunct in the management of asthma. Further trial is indicated.

DEFICIENCIES IN THE LIPOPROTEIN LIPASE SYSTEM IN ATHEROSCLEROSIS.

Pilgeram, L. O. *J. Gerontol.* **13:** 32 (Jan.) 1958.

A significant deficiency of cofactor activity in the lipoprotein lipase system has been found in the plasma of atherosclerotic patients. The deficiency sustains a progressive decline in activity with progressive chronologic age. The role of cofactor activity is discussed in reference to its serving as an index of biochemical age. For a given age group the atherosclerotic patient sustains a deficiency in cofactor activity which is in addition to the age deficiency of the clinically normal group. The curve of cofactor activity versus chronologic age indicates that all subjects will eventually have pathologic levels of cofactor activity. Albumin has been found to correct a part of the deficiency. Preliminary experiments suggest that a part of the deficiency represents inadequate activation of lipid by protein, and that there is a relation between the activity levels of cofactor and the

onset of myocardial infarction. The relation between biochemical aging and atherosclerosis is discussed. (From author's summary.)

BEITRAG ZUM KRANKHEITSBILD DER IDIOPATHISCHEN, ISOLIERTEN MYOCARDITIS, MIT BEMERKUNGEN ZUR KLINISCHEN DIAGNOSE UND THERAPIE (CONTRIBUTION TO THE DESCRIPTION OF IDIOPATHIC, ISOLATED MYOCARDITIS, WITH OBSERVATIONS ON THE CLINICAL DIAGNOSIS AND THERAPY).

Schmid, F. *Schweiz. med. Wchnschr.* **87:** 1293, 1957; through Ciba Literature Review **3:** 16, 1958.

The various forms of myocarditis include a syndrome which is characterized by a predominantly interstitial inflammation (without a pericardial or endocardial lesion), a rapidly progressive, lethal cardiac insufficiency, and frequent thromboembolic complications. This syndrome is known as Fiedler's myocarditis or idiopathic, isolated myocarditis. It is not a common disease, or at least is seldom diagnosed. The report of 1 patient in whom the clinical picture suggested this diagnosis is presented. A 45-year-old man suddenly became ill with an arterial embolism in the lower left leg. Within a few months, severe cardiac insufficiency developed. The symptoms observed—debility, a sense of oppression and anxiety, dyspnea, tachycardia, arrhythmias of various kinds, hypotension, nonspecific electrocardiographic changes—satisfied the diagnostic criteria for Fiedler's myocarditis. The treatment consisted initially of 40 mg. of Ultracorten (prednisone) daily, along with antibiotics. In addition, the patient received strophanthin, theophylline preparations, oxygen, and a salt-free diet, as well as anticoagulants because of pulmonary embolism or pulmonary infarction. The Ultracorten therapy, in combination with the classic measures indicated, was continued for one year and brought about complete regression of the cardiac insufficiency.

THE TREATMENT OF URINARY TRACT INFECTIONS WITH A SUSTAINED RELEASE FORM OF SULFAETHYLTHIADIAZOLE.

Sivak, G. C. *Am. Pract. & Digest. Treat.* **9:** 89 (Jan.) 1958.

A soluble sulfonamide, sulfaethylthiadiazole, in a sustained-release suspension was used to treat urinary-tract infections in 110 patients, as follows: cystitis, 60; pyelonephritis, 24; prostatitis, 18; postoperative infection, 4; trigonitis, 2; and infection secondary to carcinoma of the prostate, 2. Adults received 2 tablespoonfuls (4 Gm.) initially and then 1 tablespoonful (2 Gm.) every twelve hours. The dosage for children was calculated as one-half teaspoonful (0.32 Gm.) for every 15 pounds of body weight every twelve hours. No alkalis were administered. The average duration of treatment was nineteen days. Based upon the disappearance of red blood cells and pus cells from the urine and on symptomatic improvement, a good result was obtained in 85 per cent of the patients and a poor result in 15 per cent. The bacteriologic findings differed from the clinical results in that the final urine specimen was free of the original infecting organism in 66 per cent of the patients, but not in 24 per cent. The bacteriologic result in 10 per cent could not be determined because only one specimen was submitted for culturing. Only 1 patient in the latter group failed to respond symptomatically. The final urine specimens in 17 patients (15 per cent) were free of the infecting bacteria. Side-effects consisted of mild, transient skin reactions in 2 patients, abdominal cramps in 1 patient, and nausea and vomiting in 1 patient. All subsided upon withdrawal of the drug. There was no evidence of renal toxicity.

FURTHER OBSERVATIONS CONCERNING THE PROGNOSIS OF MYOCARDIAL INFARCTION DUE TO CORONARY THROMBOSIS.

White, P. D.; Bland, E. F., and Levine, S. A. *Ann. Int. Med.* **48:** 39 (Jan.) 1958.

A further analysis of 200 cases of coronary thrombosis with myocardial infarction seen in consultation between 1921 and 1930, inclusive, has shown that 7 were examined within

six hours, 14 more within two days, and 35 more within the first week, making a total of 56 during the first week. During the next three weeks, 34 more were seen, or a total of 90 in the first month. Thirty-two others were seen in the next two months, making a total of 122 patients seen during the acute attack and convalescence therefrom. The remaining 78 patients were seen in consultation at a later period. There was a steadily decreasing mortality during the first three months. Of 35 who died in the first month, 18 died in the first week and 8 in the second week. Of the 42 who died in the first three months, 26 succumbed in the first fortnight, 9 more in the second fortnight, and 7 others in the second and third months. Coronary thrombosis kills a certain, at present indeterminable, number of patients too quickly for them to be included in any clinical series. A comparison of the 25 patients among the 90 who were seen during the first month of their illness, and who survived that month and yet died within three years of the onset of their attacks, with 23 of this same group of 90 who survived five years showed that, among the former, 14 had congestive heart failure (6 had coronary insufficiency also), 7 had angina pectoris without congestive failure, and only 4 were free from evidence of either complication during their convalescence after the first month. Among the latter 23 (who survived five years), only 1 had congestive failure, 4 others had angina pectoris, and 18 had recovered completely from the acute attack, showing neither complication. The most important clue favoring longevity and a return to a normal program of life was found to be the degree of completeness of recovery after the first month of convalescence from the acute attack. Of the 24 patients who showed neither myocardial nor coronary insufficiency, 18 (75 per cent) survived five years, and the average survival of these 24 patients was twelve years. Among those who, free of complications, completely recovered from the attack, the eventual cause of death was most commonly coronary, either recurrent thrombosis or sudden death, with or without evident angina pectoris. There were no mild cases in the entire group of 200 patients, either because such cases were missed or because a consultant was not called to see them. There were 163 of severe grade and 37 of moderate grade. Not infrequently during the 1920's, the treatment and cooperation of patients such as those seen in consultation were inadequate. Our attitude concerning the prognosis of coronary thrombosis with myocardial infarction will undoubtedly be much more optimistic in the future than it has been in the past, because of 1) the recognition of mild cases, 2) the better treatment and program after recovery, and 3) the more satisfactory understanding and cooperation of the patient. (From authors' summary and conclusions.)

THE PATHOGENESIS AND MANAGEMENT OF NEUROLOGICAL COMPLICATIONS IN PATIENTS WITH MALIGNANT LYMPHOMAS AND LEUKEMIA.

Williams, H. M.; Diamond, H. D., and Craver, L. F. *Cancer* **11:** 76 (Jan.–Feb.) 1958.

Neurological complications occurred in 13.8 per cent of 5,778 patients with malignant lymphomas or leukemias. Spinal cord symptoms were usually caused by epidural lymphoma that had extended from adjacent disease. Neurological recovery was more frequent in patients with Hodgkin's disease and in those with less than complete paraplegia. In general, optimum therapy for this complication was a full course of nitrogen mustard (HN_2) followed by 3,000 r of appropriately directed radiation therapy. Although there were 11 instances of proved intracranial lymphoma, these patients more commonly had cerebral symptoms without pathological involvement, whereas those with leukemia had symptomatic lesions. Radiotherapy in excess of 1,000 r relieved signs and symptoms in 79 per cent. Cranial and peripheral nerve involvement was usually due to local compression by tumor. About half of these lesions cleared with radiation therapy. Herpes zoster was frequently initiated by presumed tumor involvement of the afferent portion of the reflex arc, and was not influenced by therapy. Diabetes insipidus, due to pituitary destruction by tumor, and exotic central nervous system infections were unusual and as a rule refractory to treatment. Intracranial hemorrhage was usually a terminal event associated with thrombocytopenia due to marrow replacement in acute leukemia. (From authors' summary and conclusions.)

NEWS AND NOTICES

POSTGRADUATE COURSE ON MEDICAL PROBLEMS OF THE ELDERLY

The University of Texas Postgraduate School of Medicine is pleased to announce a course on "Medical Problems of the Elderly" on *October 23, 24 and 25, 1958* in the Auditorium of The University of Texas M. D. Anderson Hospital and Tumor Institute in the Texas Medical Center, Houston, Texas. This course is designed to emphasize many medical features peculiar to elderly people, with emphasis on nutritional, endocrine, cardiopulmonary, neurological and emotional changes which are characteristic of this part of our population. An increasing need to understand and appreciate the problems of this group has prompted the establishment of this postgraduate seminar.

Please address all inquiries to: The University of Texas Postgraduate School of Medicine, 410 Jesse Jones Library Building, Texas Medical Center, Houston 25, Texas.